(715AB)

IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF UTAH

CENTRAL DIVISION

UNIVERSITY OF UTAH RESEARCH FOUNDATION, A UTAH NONPROFIT CORPORATION, THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA, A PENNSYLVANIA NONPROFIT CORPORATION; HSC RESEARCH AND DEVELOPMENT LIMITED PARTNERSHIP, A CANADIAN LIMITED PARTNERSHIP ORGANIZED UNDER THE LAWS OF THE PROVINCE OF ONTARIO; ENDORECHERCHE, INC., A CANADIAN CORPORATION ORGANIZED UNDER THE LAWS OF THE PROVINCE OF QUEBEC; AND MYRIAD GENETICS, INC., A DELAWARE CORPORATION,

PLAINTIFFS,

VS.

AMBRY GENETICS CORPORATION, GENE BY GENE,

DEFENDANTS.

CASE NO. 2:13-CV-640RJS
2:13-CV-643

(CONSOLIDATED HEARING)

SALT LAKE CITY, UTAH

SEPTEMBER 11, 2013

PLAINTIFFS' MOTION FOR PRELIMINARY INJUNCTION
BEFORE THE HONORABLE ROBERT J. SHELBY
UNITED STATES DISTRICT COURT JUDGE

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I-N-D-E-X

P-R-O-C-E-E-D-I-N-G-S

(9:37 A.M.)

THE COURT: Good morning everyone. We'll go on the record. This is case number 2:13-CV-640. This is our consolidated case now involving Plaintiffs University of Utah, et al. versus Ambry Genetics and Gene By Gene as Defendants.

I have your names, but, counsel, why don't we take a moment and have you enter your appearances, if you would, please.

MR. MANGUM: Good morning, Your Honor, David Mangum, Kristine Johnson, Kevin Speirs and Michael McCarthy of Parsons, Behle & Latimer on behalf of the Plaintiffs. Also Jonathan Singer and Elizabeth Flanagan of Fish & Richardson on behalf of Myriad. Mr. Geoff Biegler will also be appearing and will -- but is not in the courtroom right now. Also at counsel table and counsel of record in the case is Ben Jackson of Myriad.

THE COURT: Thank you, Mr. Mangum.

Mr. Gaede.

MR. GAEDE: Good morning, Your Honor, Bill Gaede of McDermott, Will & Emery. I'll let everyone introduce themselves individually, but I'd also like to introduce briefly to Your Honor, since we didn't have a chance to do that at the tutorial, the President and CEO of Ambry Genetics, Charles Dunlop. And also sitting behind him is the President

of Gene by Gene, Ben Greenspan.

THE COURT: Thank you.

MR. CATAXINOS: Edgar Cataxinos and Joe Walkowski from TraskBritt on behalf of Defendant Ambry.

MR. HAGEN: Good morning, Your Honor, Eric Hagen on behalf of the Defendants. I'm also at McDermott, Will & Emery.

MR. HATCH: Brent Hatch from Hatch, James & Dodge on behalf of Gene By Gene.

THE COURT: All right. Well, good morning everyone.

MR. MANGUM: Your Honor, maybe it would be appropriate for me to introduce the folks from Myriad who are here as well.

The Court: We'd be happy to have you do that.

MR. MANGUM: Thank you. Dr. Ben Roa, who is Vice President of Technology Development. Your Honor is familiar with him. He will be our corporate representative here for the purposes of the preliminary injunction hearing, and then Mr. Richard Marsh, Executive Vice President and General Counsel of the company, and Mr. Ron Rogers, who is Executive Vice President of Public Relations.

THE COURT: Thank you. Well, you'll all find those wooden benches very comfortable as we move through the day, I'm sure.

We have a lot to cover, and not a lot of time to waste,

but I want to take just a moment and step on the soapbox for just a moment. Counsel, you've all been busy, of course, preparing your arguments and preparing your witness examinations. You have a number of witnesses present who have been working on your testimony. You've all been very busy. I hope you've all had a chance to reflect for just a moment on today's date and its significance and the many privileges we enjoy in this democracy.

We're here today, of course, in an important commercial dispute between two -- well, many entities. It's a rare privilege that we enjoy here in the United States that a lot of folks around the world don't enjoy, the opportunity to come here in an open forum, in a public proceeding, to have resolution of our disputes and to apply a rule of law that guides us in our resolution of those disputes. We're deeply fortunate for that, and I hope all of you have taken just some time to reflect on that.

A few housekeeping matters. There are many people in the courtroom today who don't know this and might be interested. Counsel, of course, you all know this. We had a call last week and discussed the way that we'd be proceeding. We're here today for preliminary argument and an evidentiary hearing on a motion for preliminary injunction filed by the Plaintiffs in this case. And we'll be proceeding today, I think if counsel are still prepared to proceed this way, sort of

breaking into bits or modules the legal subject matter that we're going to tackle as part of this motion. We'll be receiving today and into tomorrow if necessary preliminary argument from the lawyers representing the various entities involved in our dispute. And then we'll be receiving testimony from witnesses who will appear here in court subject to cross-examination.

Following the conclusion of receiving our evidence, whether that's today or tomorrow, or if we have to go into another day, the parties will go back, they'll receive copies of the transcript, they'll prepare proposed findings of fact and conclusions of law that they'll submit to the court. We'll review those. We'll have the lawyers back in, and then we'll have something akin to final argument on the matter, and then we'll -- the Court will render a ruling. So that's how we'll be proceeding.

There were a number of objections filed by both sides. We have reviewed those, and let me just make a few preliminary observations about those.

There are a number of evidentiary objections that the parties filed. And I'll just refer the parties to the Heideman decision in the Tenth circuit, which stands for the proposition that at least in our circuit the rules of evidence do not apply to hearings for preliminary injunction. We will, of course, be guided by the rules of evidence, even if just in

a somewhat relaxed fashion.

And both with respect to the evidence that the parties submitted by way of affidavit or declaration, as well as the live testimony we receive during the course of this hearing, the Court will very carefully consider the evidence and give it the weight that it deems appropriate given the totality of the circumstances.

The Defendants have also invoked the exclusionary rule for our hearing today, which is proper both under rule 615 of the Federal Rules of Evidence and our local rule 43-1 subpart B. So I think the only witnesses we're anticipating calling are those witnesses affiliated with the Plaintiffs.

Is that still true, counsel?

MR. MANGUM: It is, Your Honor. Just one point with regard to that. One of the witnesses that they've moved to exclude is Dr. Roa, who is our corporate representative. Another witness that they've moved to exclude is Dr. Kay, who is an expert witness. And I believe under rule 615(c) he should be exempt from the exclusionary rule since, among other things, his presence here today is necessary for us to present the case. And also I anticipate that he will be asked questions about information of other witnesses, arguments made in presentations made by counsel, and having him present would be necessary for him to be able to respond to those types of questions.

THE COURT: All right. Certainly Dr. Roa, the corporate representative, is entitled to remain here during the testimony.

Mr. Gaede, do you have a response concerning Dr. Kay's presence during the hearing?

MR. GAEDE: Yes, just a very briefly, Your Honor. So the exclusion, the issue that Mr. Mangum raises, is that a person whose presence as a party shows to be central in presenting the party's claim or defense. Given all of the number of witnesses that are in this case, and given all the different testimony, they haven't met their showing that Dr. Kay's presence here in the courtroom is essential to them presenting their case.

And, secondly, he will be following their presentation on section 102 and 103. He's obviously had the ability to confer with counsel. So I don't see how he qualifies as being essential to preparing their case.

THE COURT: Mr. Cataxinos, did you have something to add to that?

MR. CATAXINOS: No, Your Honor.

THE COURT: Mr. Mangum?

MR. MANGUM: Your Honor, I think under the case law under rule 615 it's customary for an expert to be able to remain. I think with regard to his presence here, he's here to talk about the prior art, he's here to talk about the

science. That's going to be the discussion that we're going to have. It's what the Court is going to be asking questions about, and it will just be much more efficient for us not to have to try to tell him what was said or a question that came from the bench, and so I think we've made an adequate showing with regard to that. And the practice is for experts to be able to remain.

THE COURT: Well, and that is our local practice I think for the most part.

Mr. Gaede.

MR. GAEDE: I would just say, Your Honor, the testimony is already in the record that he's had the opportunity to look at. They are calling no witnesses of our side that he needs to hear testimony on. And so I would disagree that they have in any way shown that his presence here is necessary for them to put on their case to establish requirements for a preliminary injunction.

THE COURT: All right. Well, I think of the six or seven witnesses that we may be hearing from by way of live testimony, as I said, Dr. Roa is certainly entitled to be here as the corporate representative. Under the circumstances and given our local practice, I'm going to conclude that Dr. Kay may remain as an essential witness, and I think it will expedite the presentation of our information and evidence, and I'm confident that Dr. Kay's testimony will not be materially

impacted by his presence here in any way in terms of molding his testimony in any way.

Mr. Gaede.

MR. GAEDE: And then very briefly, I believe Mr. Mangum and I have agreed that Mr. Ford will be excluded until he testifies.

MR. MANGUM: Correct. Any other witnesses will be excluded. That brings up one additional housekeeping matter, if I may, Your Honor. Late last evening we received an e-mail from Defendants' counsel indicating that they did not intend now to call Mr. Swedlund. Mr. Swedlund, as you may -- the Court may recall, there was an evidentiary objection with regard to the foundation for a document that was an exhibit to his declaration.

THE COURT: Yes.

MR. MANGUM: We, of course, were anticipating putting -- while he was on the stand, lay some additional foundation with regard to that document. I've talked to Mr. Gaede this morning. My proposal to Your Honor is that there are three options with regard to that. One is that we can submit with leave of Court a supplemental declaration that can just provide that additional foundation. Alternatively, if they wanted to question him with regard to that, we could put Mr. Swedlund on the stand only for purposes of laying that foundation, and then they could do whatever cross-examination

they wanted to do with regard to that issue. Or, you know, if we ever had an agreement, I guess they could waive their objection to the -- with regard to the foundation on that.

THE COURT: And that objection is just with respect to the document that was attached to the affidavit, is that correct, Mr. Gaede?

MR. GAEDE: Correct, Your Honor. The witness clearly lacks personal knowledge about the document and how it was generated because he wasn't there at Myriad at the time.

THE COURT: Is there a genuine dispute that it's a business record?

MR. GAEDE: I don't know, Your Honor. They filed it in an application. They have attempted to establish that it was generated by Myriad in the ordinary course of business and they're attempting to establish that by a witness who was not there at the time and who isn't going to testify that he was present as to its preparation. So I don't know.

THE COURT: Well, we'll receive some foundational testimony then. I think this seems to be an important issue to the parties, and so let's have some foundation before we conclude. I don't -- as I think I articulated to counsel last week in our call, this is your day to present your evidence and your argument, and so we can proceed in whatever fashion the two of you have decided is most expeditious and just in terms of organization whatever makes the most sense.

Are there other preliminary matters we should address before we begin?

MR. MANGUM: That's it from our side, Your Honor.

THE COURT: All right, Mr. Mangum, I think it's the Plaintiffs' motion. Why don't you take the floor. Oh, well, is this one of the witnesses that's just leaving the courtroom? Do we have all of the witnesses out of the courtroom now who may be testifying other than Dr. Kay and Dr. Roa?

MR. MANGUM: There are no witnesses other than -- and in fact Dr. Kay is not in the courtroom yet.

THE COURT: So I guess I'm just a little bit unclear. Are there -- there are other witnesses you will be calling, but they're just not present in the courtroom; is that correct?

MR. SINGER: Mr. Swedlund is going to testify, and the other (inaudible) are not here, Your Honor.

THE COURT: I'm going to rely on someone on your side to ensure that those witnesses who are not presently in the courtroom who may be testifying understand that it's the Court's directive that they not discuss their testimony with anyone except counsel until we close this hearing, so just please make sure that that message is communicated.

MR. MANGUM: We're having a little technical glitch here I think, Your Honor.

The Court: It wouldn't be the first time in this courtroom, Mr. Mangum. Counsel, while you're working on that, so you can guide yourselves, we'll go for about an hour and a half or so, and at that point we try to give our court reporter a chance to stretch his fingers and all of you a chance to stretch your legs, and so just be mindful of that. We'll take a break. We'll figure out lunch as we get there.

MR. MANGUM: Thank you, Your Honor. I'm prepared to proceed now that we've got the technology working. Your Honor, before we -- when we discussed on the phone, the first of the modules that we're going to talk about is the presentation of our infringement case, but before we do that, just in terms of laying some overview and outline for what we'll be talking about here through the rest of the day, I have some slides I've prepared, just an overview of that.

And, first of all, I think it's important to realize the context of what we're dealing with here, particularly as we get to issues about validity and obviousness and everything else. What we're talking about today, and just so happens that it is essentially 19 years ago almost to the day that the invention -- the discovery was made of the BRCA1 gene. And to give some context to that and how revolutionary and a landmark discovery that was, it made the press throughout the country. It was on the cover of The Wall Street Journal, the cover of The New York Times. And as you got a little bit of a preview

of, it was the lead story in the news.

(viewing video)

And so, Your Honor, 19 years ago, and I think as I said, it's important that we keep that context, that we're talking about a landmark discovery and that we shouldn't be judging that development, that invention, that discovery through the lens of today as much as we should at the time that the inventions were made.

So also in terms of just kind of overview, you know, it's our view and it's certainly the law, you know, the essence of the patent right is the right to exclude others, and that's what we're here in the courtroom about today.

By statute that period of exclusion is 20 years. Myriad's had 15, 16, years on some of its patents, a little bit more, a little bit less on others, but by statute the period of exclusion that's allowed is 20 years, and we're here to preserve that period of exclusion.

And I think also important because of the mountain of paper that both sides have provided to you, and we've been through it as well, there are a lot of discussions and there are a lot of back and forth out there in the press and in the media and in the industry with regard to public policy concerns.

Now, there are certain public policy concerns that as we get to that point of the presentation we think are relevant

and appropriate, but public policy arguments with regard to that statutory established 20 year period of exclusivity we think are not. And that's supported by the Federal Circuit's decision in the AMP case, and where the court held that disapproving of patents on medical methods and novel biological molecules are policy questions best left for Congress.

So as we've said in our papers, we think there's just a large amount of material here that the Court really does not need to trouble itself with because those are issues that if someone wants to make a change in the patent laws and have some exclusion for genetic research or for medical technology, they have the ability to petition another branch of the government with regard to that.

So now with regard to the elements of our proof for a preliminary injunction, likelihood of success on the merits. The Court has received a lot of material, and we're going to be going through some of it today. But I think it's important to understand as we start that establishing the likelihood of success on the merits only requires that we prove that any one claim that is likely valid -- that is likely of being infringed is also unlikely of being proven invalid.

And as we go through the claims that I'm going to discuss with you in a minute, we think that at the end of the day it's going to be clear that there are multiple claims that they

infringe that are not subject to any serious question with regard to their validity. And that's established by the Astrazeneca case, which says for a patentee to establish that it's likely to succeed on the merits, it must demonstrate that it will likely prove the infringement of one or more claims of the patents-in-suit and that at least one of those same allegedly infringed claims will also likely withstand the validity challenge presented by the accused infringer.

Now, of course, the scope of the injunction may and would vary depending upon which claims the Court finds that we've proved the likelihood of success on. But in terms of issuing an injunction, any one claim that is infringed and is unlikely of being shown invalid is sufficient.

Now, there are three categories of patent claims that we're going to be discussing, and I'll be addressing the infringement aspects here shortly. The first is what we call the primer pair claims, and I just listed which ones those are. There's a second group of claims, all of which are method claims, that deal with detecting sequence alterations within these genes. And then the last is of the probe hybridization claims, which are techniques involved, and this court will recall from the tutorial, involved when you're dealing with large rearrangement difficulties.

So in an effort to streamline our presentation, I do have slides that we'll go through each of these, and I'm going to

move fairly quickly, particularly on the infringement issues, through these and focus mainly on the issues that have been raised by the Defendants. But as I said before, it's important to remember, any one claim that's found to be -- that we're likelihood -- we are likely to prove infringement, that's also unlikely of being proven invalid.

Finally with regard to the equitable factors that we'll discuss at the end of the hearing, I think it's important just as we go into this to realize what it is that Plaintiffs are asking for. All we are asking for is a continuation of the 15 year plus status quo up until June 13th. So all we're asking for is that during the pendency of this lawsuit, that we not upset the apple cart and not have these effects with regard to the market that we'll detail with regard to how those will be hard to unwind.

Secondly, the clear weight of the evidence I believe from the past nearly 20 years is that Myriad's contributions and Plaintiffs' contributions have benefited the public interest and have been revolutionary as those news reports indicated to helping people.

Third, and this goes to this whole issue -- we have a big battle back and forth about people's VUS rates and all of those percentages. When it comes to the issue of issuing a preliminary injunction, the public interest factor really is a prospective look from the Court's perspective. The Court

looks and says will there be some adverse impact on the public interest from continuing to have Myriad exclusivity for the period of this -- the pendency of this lawsuit?

So the issue is, is there something with regard to Myriad's current tests and the use of those tests as compared to the Defendants' test that make it such that it would be important that there be other tests other than Myriad's tests out there and available? And I submit to you none of the evidence that's been submitted in this case indicates that there is any problem with Myriad's tests in terms of being able to perform the necessary -- provide the necessary information to patients and to their medical professionals, and they have been doing that for the 20 plus years.

Finally, we need to remember, and the case law supports this amply, that because there's a limited remaining term of the Myriad patents-at-issue, that that heightens the need for preliminary injunctive relief. As a practical matter, if we are unable to obtain a preliminary injunction, the -- by the time this case makes its way all the way through the Court system, those patents will have expired, and so the only recourse Myriad has is to seek a preliminary injunction.

So now let's move into that first module of our -- of the presentation, the discussion of the infringement case. Now, I'm going to go through each of those categories of claims that we talk about, the primer pair claims and the other

claims and show how the evidence that we've presented through the declarations, and largely through the declarations of Defendants, establish each of the elements of those claims. And as I do that, I will focus on what are Defendants' arguments with regard to noninfringement.

And just as a preview to that, those arguments aren't factual arguments. They're not arguments that say where there's a dispute between Plaintiffs and Defendants over what the Myriad -- what the Ambry or the Gene By Gene processes do, they are purely and largely claim construction issues, which as the Court knows are issues for the Court and not matters upon which a factual dispute makes any difference.

Okay. So the first group are these primer pair claims. And we allege and establish that they infringe those through the process by which they generate BRCA1 and BRCA2 amplicons, the PCR process that the Court had the opportunity to learn something about in the tutorial.

Two sets of claims. The 282 patent claims 16 and 17. Those deal with the BRCA1 gene. Then similar patent claims out of the 492 patent claims 29 and 30 that deal with BRCA2.

Okay. Here is the independent claims -- well, here is the claims from the 282 patent. A pair of single-stranded DNA primers for determination of a nucleotide sequence of a BRCA1 gene by a PCR, the sequence of said primers being derived from the human chromosome 17q, wherein the use of said primers in a

polymerase change reaction results in the synthesis of DNA having all or part of the sequence of the BRCA1 gene.

And then a dependent claim from there. The pair of primers of claim 16 wherein said BRCA gene has the nucleotide sequence set forth in SEQ ID No:1. And as the Court will probably recall, that's the -- that's the sequence that has only the exons from that gene.

And then under the 492 we have similar claims, a pair of single-stranded DNA primers of at least 15 nucleotides, the sequence being isolated from chromosome 13, and the same kind of wherein clause with the same dependent claim that then limits it to the exon only portion of that.

So let's deal with the first element of those claims. And what we have here summarized on this slide is what's shown in our -- in the briefs. The admissions essentially are acknowledgment, because there is no dispute about it, that both Ambry and Gene By Gene, in Ambry's case the genomic DNA is combined with primer pairs for the BRCA1 and BRCA2 genes. That's followed by a polymerase chain reaction to produce synthetic DNA molecules for the purpose of determining the nucleotide sequencing. And then we have the citations from the brief to the proof of that.

With regard to Gene By Gene, the genomic DNA is combined with forward and reverse, so a pair of internal primers for the BRCA1 and BRCA2 genes in a PCR process to produce these

synthetic DNA molecules for the purposes -- for the purpose of nucleotide sequencing.

And it's established and agreed DNA primers are single-stranded. They're typically at least 15 to 18 nucleotides long, as the Court became familiar with at the tutorial.

So here is just your basic claim chart setting those things up side by side and dealing specifically now with the independent claims of the patents that deal with BRCA1 and BRCA2. A pair of single-stranded primers for determination of a nucleotide sequence of BRCA1. Same thing with regard to 29 except regard to BRCA2. And.

Ambry and Gene By Gene acknowledge that they use a pair of single-stranded primers, and that they use that resulting synthetic DNA to determine the nucleotide sequence of the BRCA1 and BRCA2 gene. So there's no contest with regard to the first element of the -- of these claims.

Now, on the second element, the BRCA1 and BRCA2 genes are located on the human chromosome 17q and 13 respectively. Ambry, there's the summary of the evidence that shows that the primer pairs are designed to target the breast cancer gene coding exons in the BRCA1 and BRCA2 genes. The application primers contain some sequence that hybridizes to the BRCA gene sequence so as to amplify those sequences of the exon. And then summary of the same evidence with regard to Gene By Gene.

So now here is where we have our first dispute, the second element of the claims. And importantly, however, as I indicated, the dispute here isn't about factually what does Ambry do or what does Gene By Gene do in its process. The dispute is a claim construction dispute. What does the claim terms mean, and based upon that does the admitted or acknowledged or agreed upon process come within the scope of those claims?

So claim 16. A pair of single-stranded DNA primers, the sequence of said primers being derived from human chromosome 17q. Again, Ambry and Gene By Gene's primers are derived from chromosome 17q because they are engineered to target and hybridize to, and thus there complementary to, the nucleotide sequence of a region in the BRCA1 gene, which is located on chromosome 17q. With regard to 29 in BRCA2, same proof.

And I'm going to -- we'll go through the last element and then I'll go back to their arguments and deal with the claim construction issue. So the last element of the independent claims. The evidence with regard to Ambry, they perform PCR target enrichment with primer pairs designed to target breast cancer gene coding exons that will amplify all of the sequences in the exons of the BRCA1 and BRCA2 genes, as well as at least 20 nucleotides of the adjacent intronic sequence. And that's straight out of their declarations filed in this case.

Same with regard to Gene By Gene, except they're talking prospectively. We will use forward and reverse internal primers to target all coding exons and their flanking regions. So, again, no dispute with regard to the fact that they do that.

So now let's look at their noninfringement argument. Defendants' argument of noninfringement is based on the meaning of the terms in the claims derived from and isolated from. Now, as the Court knows from either briefs, they want to take the claim term derived from and the claim term isolated from and have you construe that or interpret it by essentially just adding an adverb. They're not asking you to define -- they're not suggesting that there's some dispute about what the word derived means or in the context of this claim isolated from, they're just saying that when it says derived from, it means derived wholly from and isolated wholly from.

Well, adding terms or adding words into the claim can only take place and can only be justified if you can turn somehow to the patent and to the specification and say, all right, well, even though it says only says derived from, it really means derived wholly from and here is why. Let's look at the patent specification.

So now we turn to, and their argument is, that if you will read the word wholly into this claim, these two claims,

that they therefore will not infringe because their primers, like the common primers used in the industry, not only have the target sequence of the BRCA1 or BRCA2 gene, they also have appended to them a little tag on it that has no effect -- and I'll show you why that's the case -- has no effect on the operation during the PCR process, but then facilitates the later capturing, if you will, of those amplicons and using them at a later stage in the process.

So only if we can find something in the claim language, the patent specification, can they take that position. In fact, the claim language, the patent specification, and the case law preclude that interpretation that they're trying to propose where they want to add the adverb to those claims.

Here is the claim language. So under the Phillips case we start with the plain and ordinary meaning, how the term would be understood by one of skill. Plain meaning does not limit the claim language as Defendants propose. Derive, and these are just dictionary definitions, means to receive or obtain from a source or origin. Isolate means to set or place apart, detach or separate so as to be alone.

So these meanings indicate that the primers will have material obtained or received from a source, though it's derived, in this case from chromosome 17q, or that the primers are separate or apart from information or molecules or dictated by the chromosome 13. So neither of those plain

meanings precludes the use of appended molecules or nucleotides to the end of these primer pairs.

Now, other claim language also supports our interpretation of the claim. The other claim language requires that, quote, the use of said primers in a polymerase chain reaction results in the synthesis of DNA having all or a part of the sequence, closed quote, or, quote, all or at least 15 contiguous nucleotides of the BRCA1 gene or BRCA2 gene. So it expressly says have all or part of.

This language indicates that the primers may only have enough of a BRCA1 or BRCA2 specific nucleotide sequence to allow for synthesis of part of the BRCA1 or BRCA2 sequence. And their primer pairs clearly do that.

Other nucleotides attached to the end of a primer will not affect the ability of the pair of such primers to synthesize parts of those gene sequences. And I just want to show you graphically how that's the case.

So this -- this schematic shows what happens during the PCR process if you have primers that have no appended molecules on the end of it. And the Court is familiar with this now from our tutorial. So it goes through the -- you have the primers for the first stage. During the next stage you see that you've got the primers on one end of each of those segments. And then as you amplify that target area, ultimately you end up with millions and potentially even more

than that of these identical amplicons that have the same amplified target area and have the forward and reverse primers on the ends of that.

Now let's look at what happens if you put some appended molecules on the end of those primers. The first stage you end up with same thing, the primer plus the appended molecules. Next stage you end up with that on one side. Finally you end up with all of the various copies of it. And the amplified target area is identical, whether you have appended molecules on there or don't have appended molecules on there.

And that -- this last slide just shows here is the result of the two PCR processes, one where you have the appended molecules, one where you don't. You end up with exactly the same material functions, exactly the same way, and is literally covered within the claims of these patents.

So now let's turn to the patent specification because Phillips tells us that we look at the plain meaning as it would be understood by one of ordinary skill in light of the specifications. So what, if anything, does the specification tell us --

THE COURT: Mr. Mangum, can you go back to the previous slide for just a moment?

MR. MANGUM: You bet.

The Court: Thank you.

MR. MANGUM: And of course we'll supply -- we don't know at this stage which of these we'll use and won't use, so we will certainly supply the court multiple copies of every slide that's used.

So now we turn to the specification. The primer pairs of the present invention -- this claim is right out of the spec of these two patents -- are composed of synthetically made lengths of multiple nucleotides, i.e., oligonucleotides and Polynucleotides. Again from the specification. The Polynucleotide compositions of this invention include synthetic forms and may be chemically or biochemically modified or may contain non-natural or derivatized nucleotide bases, as will be readily appreciated by those skilled in the art. Such modifications include, for example, labels.

So right here in the specification it acknowledges what was the common usage at that time and that it was contemplated and would be contemplated that you could have these additional things on the ends of these primer pairs.

Again from the specification, quote, to facilitate subsequent cloning of amplified sequences, primers may have restriction enzyme site sequences appended to their five prime ends. So that's giving a specific example with regard to an application of using these appended -- appendages to the end, this one for the purpose of cloning.

Therefore, the specifications state that the claimed

primers can include modifications, non-natural or derivatized nucleotides, and appended molecules, including labels as merely one example. Thus, they include the use of appended bar codes, tags, and adaptors. And you can't avoid infringement by sticking these commonly understood things on the end of these primers.

Patent specifications continue. They describe the use of the adapter DNA sequences ligated onto other DNA and the use of such adapter sequences to prime a PCR amplification reaction. These adapters are described as having tags attached in the form of biotin is one example that allows for later analysis by a specific capture of the nucleic acids generated by use of the primers.

So we have all of these examples straight out of the specification of the use and discussion of, and with regard to this last one with regard to probes, that you can also attach a label or reporter molecule, and that suitable labels and methods for labeling probes and ligands are well known in the art.

So all of it is contemplated in the patent specification, and there's nothing there in the patent specification that would lead you to believe that only those -- only nucleotides that come right out of BRCA1 or BRCA2 can be used as part of these primers and that you can't put appendages on them.

Here is the case law that's important on that.

Because -- and interesting -- well, maybe interesting to me. But my first patent case was Amstar Corp. versus Envirotech in front of Judge Jenkins. And what that case stands for is that you can't avoid infringement by merely adding something to someone's claim.

If someone has -- and just to use a very basic example, if I had a patent on a piece of wood with a graphite down the middle of it that you could use as a writing implement, a patent on a pencil, you couldn't avoid infringing that by putting an eraser on the end and saying, well, I have a pencil with an integrated eraser on the end of it, therefore, I'm not infringing your patent. You'd still be infringing my patent. And while you may be able to even patent that combination, you can't practice what I have without getting a license from me.

So modification by mere addition of elements cannot negate infringement without disregard to the long-established hornbook law. Adding nucleotides to a BRCA1 or BRCA2 specific primer to facilitate later sequencing does not change the fact that part of the primer's sequence is derived from chromosome 17 or isolated from chromosome 13.

Now, I want to take just a minute and say -- to go to the subsequent -- the supplemental declarations they filed on this point because, frankly, you know, we get a second declaration from Mr. Elliott, we get a separate declaration from Mr. Mittleman. Those declarations add nothing new to this

dispute. They don't factually dispute what their process is and what the primers look like. They essentially repeat or elucidate to upon what they said in their first declarations.

So with regard to Mr. Elliott, he reiterates that Ambry uses appended molecules on its primers. They're tags, adaptors, etcetera, and he illustrates those. So, okay, fine. There's no dispute with regard to that. But for the reasons I've just indicated, that's legally irrelevant. It only goes -- it's only helpful to them if they get a claim construction that says derived doesn't mean derived, it means wholly derived from.

So then he makes the point, well, the appendages that you talk about in terms of specific examples within your patent don't include the specific types of things that we use. Well, again, you know, those statements, those examples, are not restrictive. So the specifications don't state -- they do not state that the claimed primers are limited to the specific examples described, therefore, it makes no difference. And legal precedent also then refutes what Doctor -- apologize for saying Mister before -- Dr. Elliott indicates.

Under Phillips, although the specification often describes very specific embodiments of the invention, we have repeatedly warned against confining the claims to those embodiments because persons of ordinary skill in the art rarely would confine their definitions of terms to the exact

representations depicted in the embodiments.

So the specifications very commonly provide an example. They're not exclusive. Even your preferred embodiment, as the Court knows, is not limiting unless there's something specifically called out in that claim that says I mean this and only this to the exclusion of everything else.

The other thing that Dr. Elliott does in his declaration is to reiterate the argument or the fact we pointed out earlier. We do two PCRs at Ambry he says. You know, in the first one we use primers like the ones you're talking about, in the second it's part of our sequencing. We do another PCR, but we use nonspecific primers that are not specific to the BRCA1 or BRCA2 genes. We're only alleging infringement of that first primer pair, not what they do subsequently, so that's just not responsive.

So now let's move to the dependent claims that come off of those claims, claim 17 and claim 30. And those dependent claims, as the Court will recall, those are the ones that then limit themselves down to the exon only sequence of the BRCA1 and BRCA2 genes.

So here is essentially Ambry and Gene By Gene's argument. Ambry and Gene By Gene acknowledge that among the primer pairs that they use, and that they then use to amplify and sequence the BRCA one and BRCA2 genes, some of those primer pairs have introns -- intron regions on them as well as exon regions, but

because the BRCA1 and BRCA2 genes have some exons that are so long, at least some of the primer pairs that they use match up only to an exon region of the BRCA1 or BRCA2 genes.

And our view then is on these dependent claims, not all of their primer pairs will infringe these dependent claims, but those that are directed at exon only regions do. And this just shows that that's what they're doing, and that's also a Gene By Gene, tends to the amplify all exons, therefore, those that are the larger ones that are too large for the Sanger sequencing, they're going to need to use tiled amplicons and do what I just described.

And then this little graphic here just shows that because of the length of some of these exon regions, you're going to end up using primer pairs that come only out of the exon regions.

So then here is the claim chart matching up that for claim 17 and 30, that at least some of their primer pairs will include and be complementary to only exonic regions and therefore infringe claim 17 and 30.

SO there's really no dispute with regard factually to what Ambry does and Gene By Gene intends to do and therefore we have infringement of those claims. They don't deny that to amplify and sequence the BRCA1 and BRCA2 genes there will be at least some primers and amplicons that will not have intronic sequences.

Okay. That deals with primer pairs, so now I'm going to move on to the allegations of infringing claims that deal with sequencing, essentially detecting these variations in the sequence of the gene.

Methods for determining alterations in the BRCA1 and BRCA2 genes. We have the 441 patent. Claim eight deals with BRCA1, the 857 patent, claim four, deals with BRCA2.

Now, here is, again, just follows that same pattern. Here is the language of the claims. And as the court will recall, claim eight that we're asserting is a dependent claim, and so to show infringement of that dependent claim, I have to show first that all of the elements of the independent claim from which it depends are also net, as well as the additional elements that come from claim eight. And the 857 patent, claim four, those are the elements with regard to it.

So now let's talk about what Ambry does. And, again, no dispute between the parties about factually what takes place. Ambry does both next-generation sequencing and Sanger sequencing. And the Court had the opportunity to learn a little bit about that during the tutorial.

So Ambry performs next-generation sequencing of all coding exons, plus at least five bases into the five prime and three prime ends of all of the introns and untranslated regions of the BRCA1 and BRCA2 genes.

Specifically Ambry -- Ambry's BRCA sequencing tests

utilize primers that amplify --

(THE COURT REPORTER ASKED COUNSEL TO REPEAT)

I'm sorry. Amplify the sequences of the exons and at least 20 base pairs. And that comes just directly out of it. And maybe so I don't blow up Ray's fingers, I won't read everything that we're all looking at at the time and try and be a little more summary in that presentation.

So Ambry performs both Sanger and next-generation. We allege that both of those types of sequencing infringe. Gene By Gene does Sanger sequencing, and we allege that that infringes, and this is the support that shows that Ambry performs the Sanger sequencing and that Gene By Gene, again prospectively they say, will utilize PCR to amplify from patient genomic DNA all coding exons and the 50 base pairs of nucleotides of intronic sequence flanking each exon.

And then as the Court had the opportunity to learn in the tutorial, Sanger sequencing uses these dideoxynucleotides to stop that process. And as you sequence the BRCA1 gene, you're going to include all of the nucleotide positions, and that becomes important in some of the subsequent claims.

So the analysis of the sequence. Ambry and Gene By Gene compare the patient's entire human genome sequence, which includes the BRCA1 and BRCA2 genes, as deduced in the sequencing operations. And they compare that then to a reference or wild-type.

Now, And I'll deal with -- this is essentially their noninfringement argument. They say, well, you say you use these techniques to sequence and analyze the sequence of the BRCA1 and BRCA2 genes. Well, we compare and analyze the entire human genome. We sequence everything and we look at everything, as we get to with regard to these slides. Everything includes the BRCA1 and BRCA2 genes.

And so it's a very similar argument to what we were talking about before with regard to Amstar. You can't avoid infringement by saying, well, I do what you say only you can do, but I also do some other things at the same time.

So Ambry locates all the identified variants, and then classifies them as either benign and does mutation detection. Same thing with regard to Gene By Gene.

So here we now compare element by element the claims that are asserted, along with the proof of what it is that Ambry and Gene By Gene do. With regard to the first, they perform this step of comparing the germline sequence of the BRCA1 gene. And here we have an argument from them, and we'll deal with that as it becomes another claim construction argument, about whether or not using synthetically created, synthetically generated amplicons comes within the scope of this claim.

So other than that dispute with regard to does it cover synthetic amplicons and, two, does it -- if I compare

everything, not just the BRCA1 gene, they acknowledge that they do this step.

Claim eight, again, wherein a difference in the sequence of the BRCA1 gene is -- to a wild-type is determined. And other than disputing whether or not there's synthetic amplicons coming out of PCR qualify under this claim, they don't dispute what we say they do.

Next element of these claims, wherein a germline nucleic acid sequence is compared by amplifying all or part of BRCA1 gene from said sample using the set of primers and then sequencing. They acknowledge that they -- both Defendants acknowledge that they do that. Same with regard to those comparable elements in the 857 patent with regard to BRCA2.

So let's turn to their noninfringement argument. And, again, the important thing here, there's no dispute about -- factually about what they do. It's just an argument about what does the claim mean, which is an issue that the Court has full control over and is an issue for the Court.

So Defendants assert that they do not analyze the patient's, quote unquote, BRCA1 gene because they do not utilize patient mRNA or cDNA. So essentially their argument there is, well, we, like you, we use that -- the PCR process and we use those synthetically generated amplicons to perform this analysis. And their argument is that our claims with regard to the definition of BRCA1 gene is somehow limited

not -- and does not include those synthetic versions.

Again, now, we have to look at the claim language and we look at the specification. And Defendants' argument is contrary to the claim language and to the patent specifications. The claim language requires use of a BRCA1 gene or a BRCA1 RNA from a tissue sample from said subject or a sequence of BRCA1 cDNA made from mRNA. BRCA1 gene from a tissue sample from the patient can be used not only in RNA or cDNA made from mRNA.

Now, what do those terms mean? The patents state that the terms, quote, BRCA1 gene and, quote, BRCA2 gene refer to Polynucleotides and that the Polynucleotide compositions of this invention include RNA, cDNA, genomic DNA, synthetic forms, and mixed polymers, among others. So by definition the patent -- the patentee can be his own lexicographer. He can define terms the way he wants.

By definition, the claim terms BRCA1 gene and BRCA2 gene include all synthetic forms of DNA, which essentially eliminates Defendants' noninfringement arguments. That includes all primers and the amplicons that they produce. Defendants don't deny that they are using the sequence of the BRCA1 and BRCA2 amplicons produced from PCR. And our position and that support from the spec is that that use is encompassed by the claim language. Okay. That's their first argument.

Their second argument is we compare patient sequences to

the sequence of the entire genome, not only in BRCA1 or BRCA2 genes, therefore, we don't infringe. Well, the claims in the patent do not exclude additional sequencing and do not define additional sequencing as mutually exclusive from what the claims require.

The claims use the transitional word comprising, which has significance in patent law. Means that the claims are open-ended and inclusive, and thus they encompass anything that includes additional actions or steps beyond those required in the claims. And defendants acknowledge that law.

A claim using the, quote, the single comprising is generally -- the signal, excuse me, comprising is generally understood to signify that the claims do not exclude the presence in the accused apparatus or method in addition to those explicitly recited. Then again this whole Amstar notion that we talked about earlier.

Now let me talk about this case that they rely on. They rely on the Dippin' Dots case, and we recited what the general case law is on this. This is a unique case that's just totally inapplicable in this area.

In the Dippin' Dots case there was express statements within the patent specification where the patentee -- and this is language from the Court -- had narrowly defined the claim term at issue, beads, and the term could not be broadened because the patent made clear that the process at issue must

produce beads and only beads and could not include production of irregularly shaped particles.

So under those unique circumstances where you had a patent that said -- here it would be the equivalent of saying, you know, you can -- it would be analyze and compare the BRCA1 and BRCA2 gene sequence, but in all -- but don't look at the rest of the human genome. That -- that expressly excluded from the scope of this claim is looking at the entire human genome, including BRCA1 and BRCA2. That's just not the case here.

So Defendants cite only statements that analyzing the BRCA1 genes means that the BRCA gene sequence must be analyzed for various possible variations and mutations. They point to no patent language that BRCA1 and BRCA2 gene sequences must be analyzed to the exclusion of others in all instances. And then that's the general case that applies that principle, with Dippin' Dots being the exception.

So I'm now going to be really very quickly here. With regard to these -- analyzing the claims that deal with detecting these modifications and alterations, there is a subset of those that deal with very specific regions within the BRCA1 and BRCA2 genes that's called the omi haplotype claims.

And essentially our infringement position with regards to those tracks the earlier one. Their noninfringement arguments

are essentially the same, as I'll show you, and so I'm not going to take the time, unless the Court has some specific questions with regard to those claims, to deal with -- with each of the different elements.

THE COURT: I understand your argument on that.

MR. MANGUM: Okay. That's just calling out what the claims require. And, again, we don't have a dispute here with -- that Ambry and Gene By Gene look at those regions and perform that function. So essentially then, you know, again, uses the term comprising. The arguments are the same with regard to those claims.

So, finally, the final group of claims are their -- are assertions against Ambry with regard to infringement by large rearrangement analysis. And this is where we get into the multiarray, MLPA, that we talked about during the tutorial.

Two claims that deal with hybridizing a BRCA1 or BRCA2 gene probe, 441 patent claim seven that we've asserted, and that deals with BRCA one, 857 patent claim four that deals with BRCA2.

The 441 patent claim seven is identical to what we discussed before on claim eight, except that instead of requiring that the comparison includes amplifying with a set of primers and sequencing the amplified product, it requires the comparison of a patient's sequence to a reference sequence that includes hybridizing a BRCA1 gene probe which

specifically hybridizes to a BRCA1 allele, which we talked about at the tutorial, to genomic DNA isolated from said sample and detecting the presence of a hybridization product wherein a presence of the said product indicates the presence of said allele in the subject. And 857 essentially the same with regard to the BRCA2 and in substance.

So what does Ambry do? And here this assertion of infringement is only against Ambry. We don't have any information with regard to Gene By Gene and the techniques that they intend to use here, so we have not asserted any current infringement claim against them with regard to that.

Ambry's large rearrangement analysis looks for large deletions and duplications of nucleotides, and they have two types of tests. They either use MLPA or a comprehensive full-gene gross deletion/duplication analysis, part of which is the BRCA1 and BRCA2, and then microarray analysis to detect large rearrangement. And the citations showing that that's what their tests do are here in our briefs.

So Ambry's MLPA, microarray processes use synthetic probes targeting the exons or flanking intronic sequences in the BRCA1 and BRCA2 genes. The probes are complementary to, and thus hybridize to, their respective target section if that section is present and has the same nucleotide sequence. And the probes are specifically targeted to the wild-type BRCA genes and thus are specific for the wild-type alleles.

So, again, those are the steps in the patent, and they perform those steps. Let me get to their assertions with regard to noninfringement. Here is Ambry's argument. Ambry says we don't infringe 441 patent claim seven because we do not use probes that are specific for any known variations of BRCA1 that predispose the patient to certain cancers.

So what they're saying there, they're saying, well, when we do this analysis, our probes aren't designed specifically to capture some of these mutations within the genes. Our probes are designed to go for the wild-type probes. So the problem with that is these patents specifically cover using probes that are designed to catch the wild-type alleles. So the fact that they do that, which they acknowledge, is enough to prove infringement. That -- that our claim also says if you do that to try to catch a mutated gene, you will infringe us is just of no moment here.

So quoting the patent specification, Ambry admits that the language, quote, a BRCA1 gene probe which specifically hybridizes to a BRCA1 allele should be interpreted to mean a BRCA1 gene probe that hybridizes either to the wild-type BRCA1 allele or a sequence of a known mutation of the BRCA1 gene sequence which predisposes to certain cancers. That's right in their opposition brief. And in Elliott -- in Dr. Elliott's declaration they admit that they use probes that are specific for the wild-type BRCA genes.

So Ambry asserts noninfringement of these two claims because they say the reference to the BRCA gene and BRCA1 gene and BRCA2 gene in those claims requires that the entire genes, including all the introns and exons, are screened. So, again, this is a claim construction argument. It's not a dispute about what they do. It's their argument that this claim should somehow be interpreted to exclude what they do.

Ambry then argues that Plaintiffs have not demonstrated that Ambry's large rearrangement tests screen for rearrangements in all portions of the BRCA1 and BRCA2 genes. Our position is that's based on erroneous claim construction, and once you properly construe the claim, then infringement is clear.

The terms BRCA1 gene and BRCA2 gene are not limited in the manner that Ambry asserts. The patents define both terms to include expressly fragments and portions of each gene, not all portions of those genes.

Here is the language out of the 441 patent, defines the term BRCA1 gene as, quote, Polynucleotides, all of which are in the BRCA1 region, closed quote. That definition demonstrates that the term means some number of nucleotides in the BRCA1 region, not that every nucleotide in that gene must always be included. Specification does that. So we look at the claim language. We look at the spec.

These terms, when applied to nucleic acid, refer to a

nucleic acid which encodes a BRCA1 polypeptide or fragment, and that the nucleic acids of the present invention will possess a sequence which is either derived from or substantially similar to the natural BRCA1 encoding gene or one having substantial homology with a natural BRCA1 encoding gene or a portion thereof.

So throughout the specification, BRCA1 gene, BRCA2 was not defined to be -- or require the entire gene. It's the gene or any portion thereof. And with that understanding, as set forth in the patent and specification, then what they -- what Ambry admits it does infringes.

So just to sum up, Your Honor. I'm through with that first module. So on the primer pairs, what's required, and we have a coordinated pair of synthetic molecules, and they perform each of those steps in their method. And with regard to the method claims, we've laid out again how they infringe those. We need only show infringement of one claim. We believe we've established a likelihood of success on each of these claims.

They're noninfringement arguments in our view fail. They're based on erroneous claim constructions, as we've pointed out. And they try to avoid infringement by arguing that they do more than the claims require, and that's just a legally insufficient basis to try to avoid infringement. Thank you, Your Honor.

THE COURT: Thank you, Mr. Mangum.

Mr. Gaede.

MR. GAEDE: Your Honor, I'm going to get right to it because we'll be addressing those other issues that were raised in Mr. Mangum's opening later on in our presentations. I don't see the point of going to it now, except just to point out that the subject matter in the NBC News report is unpatentable subject matter. The gene itself is, of course, not patentable subject matter.

Let's start though here with infringement. First of all, it's their burden with pinpointed evidence. And, you're right, there are claim construction issues here that you are going to have to resolve. It's not largely disputed in many respects how next-generation sequencing, amplification and sequencing works. And we'll talk a little bit about that, but the bottom line is it's a claim construction issue in a couple of different places, and we'll focus in first, as Mr. Mangum did, on the primer claims.

I think it's important to point out too as well that they have to find literal infringement because they have not argued Doctrine of Equivalents in their briefs and therefore they have waived that argument. So they must show it is more likely than not that Ambry and Gene By Gene literally infringed the claims.

All right. I think again the basic rules of claim

construction, Your Honor knows them in the Phillips case, but it's important here because I noticed in Mr. Mangum's presentation he was glossing over the plain language of the claim. And it's the claim that defines the invention. And it's important that we focus in on the claim, as well as the specification, as well as, of course, there's any prosecution history evidence, citing them. And then, of course, extrinsic evidence is admissible only if there's an ambiguity.

But the primary language, the primary governor of what is within the scope of this claim and what these claims comprise is the claim language that is drafted. And why is that so important? Because that's what the patentee puts the world on notice of is the scope of their invention.

And what you have here is the scope of an invention that reflects the state of the art in 1993, 1994, and what they're trying to do now is expand it out to cover -- which as you heard at the tutorial, next-generation sequencing wasn't developed until the 2000s, of course as you'll hear today at some point, I'm sure, the human genome wasn't even sequenced until 2000 or 2001. So let's get to the claims themselves.

Again, let's go ahead and go right to the claims. Now, Mr. Mangum focused on derived from human chromosome 17q, but what's important is that he glossed over the issue of nucleotides and says where the language of the claim -- which clearly is limited because it doesn't use the word comprising.

It says the sequence of said primers being derived from human chromosome 17q.

What does that introduce? That is a structural limitation by reference to a source. This is a structure, this is a composition of matter, and it defines the structure of the primer by reference to this source. And it's well accepted in the case law that you can define a composition of matter, a structure, by reference to a source. And that's exactly what they're doing here.

Note that it doesn't say a pair of single-stranded DNA primers for determination of a nucleotide sequence of a BRCA1 gene by a polymerase chain reaction. The sequence comprising -- or the sequence of said primers comprising nucleotides being derived from human chromosome 17q. It modifies the entire element of primers, and it puts in place a structural limitation by reference to that source.

The same is true of claims 29 and 30 of the 492 patent. That makes it even clearer because it says the sequence of said primers being isolated from human chromosome 13. Structural limitation in the claim defining the structure of the primers by reference to this source.

Now, I don't need to go through their chart. I think we all agree that they are not contending that our primers are isolated from 17q as a whole. It's undisputed. And that means we do not literally infringe the structural limitation

of those claims.

Go on here a little bit. So what do they do? They argue in the plain claim language, and it's the plain claim language that has primacy. They also cite to irrelevant portions of the specification. I would also submit that their -- they introduce evidence from the dictionary that confirms our construction as well.

I'd cite to the Court the Amgen v. Hoffman-Laroche case at 580 F.3d 1340, 1367. And that is the case where a structure was defined by reference to a source, i.e., it must be -- in this particular case it's referenced to the source of being purified from certain mammalian cells. I can get into and explain to you why that was important, but the bottom line was that it was to distinguish the Amgen composition from the naturally occurring composition. And they did that by reference to how it was made, i.e., a source limitation that defined a more defined set of structures.

That's what those claims do, those primer claims. They define the structure of the primer in the claim by reference to the source. And that's well accepted as a way to claim within the patent law. But what isn't well accepted in the patent law is to define a claim by reference to a source of a structure and then to say but we only mean part of it. There's no language in the claim that says that.

And think about the implications of what they are

arguing, Your Honor. You could have three or four nucleotides in a primer. The rest of it could be 20, 30 nucleotides, clearly not isolated from another chromosome -- from the referenced chromosome, clearly not, and they would lay claim to that through their reading of the patent claims. It's an incorrect reading of the claim, and they need to be held to the structural limitation by the reference to source they put into the claim. And they certainly could have drafted it differently had they meant a different -- had a different meaning.

So also as you can see in their dictionary.com definition, it means it comes from the source of origin. It doesn't mean part of it comes from the source of origin. It means it comes from the source of origin. And it's limiting language of the claim.

So let's take a look. This is -- Mr. Mangum referenced a few arguments here, and he talked about some of the language with amplification and cloning. But I think this language in the specification, which they rely on as well, proves our point exactly. Look at how this language is used. So it says in order to facilitate subsequent cloning of amplified sequences, primers may have restriction enzyme site sequences appended to their five prime ends. Okay. That's another structure that they're not claiming.

But what do they go on to say? Thus, all nucleotides of

the primers are derived from BRCA1 sequences or sequences adjacent, except for the few nucleotides necessary to form a restriction enzyme site. So here they acknowledge that derivation refers to just the sequences itself, and then it says except these other ones. They're not swept under the language of derived by reference to the source. And so here they're using the term derived in the way that the claim uses it as well to define a set of structure of a primer by reference to that sequence in the chromosome.

They also talk about adding labels. You remember Mr. Mangum making that argument. A label is not the sequence. A label is you put like a florescent tag on it. That's not a sequence. That's not adding sequence, i.e., the sequence is still the same even though you add a label to it. So it doesn't change the fact that the sequence comes from or it must come from chromosome 17q or chromosome 13 in the case of the 492 patent.

Now, Dr. Elliott has provided additional information to you on this, just to make this point, that the modifications do not add the nucleotides to primers, that they either modify or they substitute a non-natural nucleotide.

Then they also go to adapters. Again, Dr. Elliott -- I'm going to go through this quickly because it's all evidence in the record, all of which establishes a substantial question of noninfringement. Again makes reference to adapters. Those

are not part of the PCR primers, the section in the spec that they're referring to. Universal primers, not part of the PCR primers. And as Dr. Elliott tells you, that the patent here describes a section of the probe and addresses their argument. So you'll have those, and we'll give you a set of these slides.

So when we're adding the word wholly, what we're trying to do is to prevent the misconstruction of the claim that Plaintiffs are attempting to argue for by reading out the structural limitation of the claim that makes clear that the primer must be defined, the sequence of said primer with reference to the chromosome.

So that's why it puts the word wholly in there because all you're doing is giving meaning to the structural limitation introduced into the claim by reference to the source, i.e., the sequence that occurs on chromosome 17q or chromosome 13, depending upon which claims you're looking at.

No question, of course, that our primers contain sequences other than the human chromosome sequence. I don't think we need to go into this in too much detail. I think that point is undisputed.

I will though -- I think it's important just to kind of take a quick look at this slide right here. This is in Dr. Elliott's second declaration, and it references exactly what Ambry does to explain this point. You'll see in the

first round of PCR the primer is a composition of some nucleotides from the chromosome sequence, some from clearly artificial other -- other -- not sequences related to chromosome 17.

You make a PCR product that is a combination of the two. You then come in with a second round of primer that is completely -- doesn't in any way even bind to the genomic sequence in the second round, purely artificial. They're reading -- I don't know if they're reading that act as an act of infringement, but clearly that can't be an act of infringement to use those types of primers. And then you get your PCR product, which you can see here is a combination of different types of sequences.

THE COURT: I got it. And I'm confident -- Mr. Mangum will tell me if I'm wrong about this. They're just focused on the first round. They're not alleging infringement in the second round of PCR.

Am I right about that, Mr. Mangum?

MR. MANGUM: That's right, Your Honor.

MR. GAEDE: Okay. What about the case law? Case law is pretty clear. The limitation that follows is not prior to the word comprising in this claim. It's a structural limitation of the claim in and of itself of the structure of the primer. So the cases that they rely on about additional elements or comprising -- let's take Mr. Mangum's analogy of

the eraser and the pencil.

What is being described here is not a primer that defines eraser and the pencil. The primer itself is the eraser, and the primer itself must be all those sequences from 17q or chromosome 13. And so the fact that you attach that eraser, which does not infringe, to a pencil is irrelevant because it goes to the issue of the structure of the eraser itself.

Another example is a motor in a car. If you had a claim to a motor and you put that in the car, he has it right, if the claim is addressed to the motor, you don't defeat infringement by putting the motor in the car, just like you don't defeat infringement by putting an eraser on a pencil. That's correct.

But that's not what this claim says. It doesn't have a language of comprising. It says has a language of limitation. In and of itself said sequence of the primer being isolated from or being derived from the chromosome itself. So the claim itself is addressing the motor, i.e., it's a six cylinder motor, and the claim is addressed to a six cylinder motor. We don't have a six cylinder motor. We have a new type of motor. My analogy is going to run out on me here, Your Honor. But we have a new type using next-generation sequencing that didn't even exist back then. And so we do not infringe, not because of the additional elements issue. We're not making that argument. The motor in itself, the structure

of the primer in and of itself is defined by the claim.

Amstar is the same thing. Amstar was a process claim where there is comprising language. That's not the issue here, different case law, means plus function, apparatus claim.

Okay. Let's move on to -- are there any questions on that, Your Honor?

The COURT: There's not.

MR. GAEDE: Okay.

THE COURT: And we'll go another 15 or 20 minutes before we take take a short break. Go ahead.

MR. GAEDE: Okay. So claim eight. Now, I think it's important here as well that you focus a little bit also on claim one, which is invalidated by Judge Sweet and also by the Federal Circuit.

THE COURT: Oh, we have to; right? This is a dependent claim.

MR. GAEDE: Exactly. And what's important to recognize is in this independent claim it requires a mental comparison of comparing the sequence. And what it requires is a comparison of sequence for the mental step exactly and an intention to compare directly to the BRCA1 sequence. Now, why is that true? Because we know the state of the technology at the time. That's what they could do. They couldn't compare it to a whole genomic sequence because the whole genomic

sequence didn't exist. The mental step of the comparison didn't exist in 1993 and 1994 when the patent application was filed.

So what do we have here? Amplifying all or part of the BRCA1 gene from said sample using a set of primers. Yes, we, of course, do amplify some sequence, but we don't perform the mental comparison step of claim one.

So it's not -- it's not disputed that we don't use cDNA, that we don't use mRNA. What we're arguing about is the claim required a direct mental step comparison to the wild-type BRCA1 sequence or to the genomic sequence, which is the mental step that is undisputed that we do.

Now, it also has the definite article "the", making reference to the BRCA1 sequence, the BRCA1 gene. Indicates an alteration in the BRCA1 gene, said subject. And so the specification also makes reference too that it's the invention of comparing to the BRCA1 sequence, not to the genomic sequence of the human as a whole. And then again the specification makes reference of comparing to just the BRCA1, the wild-type, not to the genomic sequence as well.

So they don't dispute that we amplify and sequence exons and a few bases of the introns, and that we compare the patient exon in flanking intron sequences to the entire human genome. We do that for a reason too, Your Honor. It's not just sort of a cute design around argument, quite frankly.

There actually are the issues of pseudogenes which you raised in the hearing earlier during the tutorial. And there can be pseudogene sequences elsewhere in the -- in the genome of the human being and that can be detected through -- by nonspecific amplification, so you want to take those out. So there's not only just an argument, mental step, is that what we're doing is comparing to just -- comparing to the human genome, but there's also a legitimate reason for doing that, which is to remove any of that sort of confounding factors or irrelevant data from the comparison.

And, again, I don't think there's any real dispute here that the limitations have to read literally on the accused process. We have to literally -- we have to literally compare the two sequences, and we literally do not compare the two sequences. We compare to the genomic sequence as a whole.

Going on to the 857 patent claim four. This is essentially the same issue that we just talked about. Mr. Mangum's correct on that, that essentially is the same issue that you need to resolve. And for the reasons we just stated, we don't practice this claim.

Again, just noteworthy, claim two, of course, is an invalidated claim, and it's a mental comparison, and that's really what is being looked at there.

Let's take a look here at the 721 patent claim five and 155 patent claims two and four. So here -- here is the point

that was glossed over in the claim. And, again, it's the claim language that governs. If you look in the claim where it says comparing the determined nucleotide sequence from said female individual to SEQ ID NO:263 -- and I hate to say this, Your Honor, but SEQ ID NO:263 is essentially the cDNA sequence. Like in the other claims you have SEQ ID 1, this is the cDNA sequence, the coding region sequence only.

Now, of course, the coding region as a sequence doesn't exist in nature. In other words, the -- it exists as with introns, exons, it is the entire genomic sequence. So the coding region sequence as a contiguous linear sequence does not exist in the natural genome for BRCA1 or BRCA2. So do we compare the nucleotide sequence from the female to the cDNA sequence? No. We compare it to the genome.

Here, again, same thing in claim two and claim four of the 155 patent where you're comparing the sequence to the sequence of the SEQ ID NO:1, which is also the cDNA, the coding region sequence. That, of course, doesn't exist naturally in the human as a contiguous sequence.

And, again, there's no evidence that we in performing that mental step literally compare the patient's sequences to the contiguous cDNA sequences, therefore, no literal infringement. Same case law.

Now, this is another noninfringement argument just for Ambry on 155 patent claims two and four. You'll see here in

claim two and claim four -- and of course this follows the comprising language so these are limitations of the claim that you have to perform. You have to -- it says (b) sequencing said amplified fragment by dideoxy sequencing. And then it goes on to say repeating steps A, amplifying, and B, i.e., sequencing by dideoxy sequencing, until said individual's BRCA1 coding sequence is completely sequenced. So what that means is you have to use dideoxy sequencing for the entire sequencing, to sequence the entire BRCA1 coding sequence is completely sequenced. That's a limitation of the claim.

So, first of all, they don't contend that the next-generation sequencing is dideoxy sequencing. Instead, they point to the Sanger sequencing that Ambry does use in part, and that evidence is right here in front of you by Dr. Elliott.

So what happens is if there's a variant identified, Ambry will only sequence by dideoxy sequencing, i.e., Sanger, just that part. It's not going to sequence the entire coding region sequence. And so we do not Sanger sequence the entire BRCA1 or BRCA2 sequence as the claim requires. It's an additional ground of noninfringement for Ambry.

I agree with Mr. Mangum that they've only asserted large rearrangement analysis against Ambry. Gene By Gene is not accused so the preliminary injunction could never rest on infringement of these claims that follow against Gene By Gene.

There's no contention.

So come to claim seven of the 441 patent, and it comes down to this very specific issue. It's undisputed that Ambry does not use mutation specific probes for purposes of detecting an alteration in the allele, I.e., the probe of a mutation. Your Honor understands mutation will be a change in a nucleotide sequence, and that means you're going to have a probe that is specific for that mutation. And you're going to come in, and under the Watson-Crick natural base pairing it's going to detect, affirmatively detect, that mutation by using that type of probe.

Specifically hybridizes to a BRCA allele to genomic DNA isolated from said sample and detecting the presence -- the presence of a hybridization product wherein a presence indicates the presence of said allele in the subject. So it's a method for screening for the alteration, claim one. That's the invalidated claim. Presence of the hybridization product indicates the presence of the alteration. Ambry does not use a probe that affirmatively binds to the alteration, the mutation in the gene, to detect that presence.

And we could actually in large rearrangement analysis. You could have -- you know, you remember from the -- from the tutorial that there are pieces of the DNA that -- larger pieces that are essentially just missing. We could certainly have a probe that would come in and just probe where that's

missing by having it detect the gap, if you will, because you've taken the gap out and then having a probe that hits both sides where the deletion will have dropped out and that will come together. So you have a probe that would then bridge that. No question that would be specifically hybridizing to the mutation and detecting it, but that's not what the claim -- that's not what we do. All we do is we use probes that go to the wild-type and do not specifically hybridize by definition to the mutation.

So, again, the definition in the claim, probes: Polynucleotides, polymorphisms associated with BRCA1 alleles which predispose to certain cancers, i.e., mutations, or are associated with most cancers, i.e., again, mutations from the wild-type, are detected by hybridization with a polynucleotide probe which forms a stable hybrid with that of the target sequence under stringent conditions, i.e., you're probing for the mutation.

And that will tell you, if you have it there, that you have a predisposition to cancer because you have affirmatively detected that that exists. Also have the probes are allele specific. And they're right that we do not affirmatively detect the mutation. And that's what the claim requires, and they need to be held to the scope of their claim, and they also need to be held to the scope of what they write in their specification because that's what they tell the public.

That's the public notice function of claims.

And in essence -- and we'll get to this in the next time -- if you find that the claim is that broad, that they preempted any probing, you cannot probe the BRCA1 gene. Can't be done because you're going to detect mutations, you're going to detect wild-type. Those are the two other types of polymorphisms. In essence, they're reading the claims so broadly that it preempts the gene itself. We'll get to that in the next section, but that's in part the problem that exists with their claim.

So the claim requires an identification of a variant through actual hybridization of a probe specific for that allele. We do not probe to any specific allele. The probes don't tell what if any mutation or rearrangement the patient has. It just tells the clinician that the wild-type BRCA is present, and therefore there's no literal infringement.

I won't at this point -- let me just cover one last point here. Again, they're arguing -- same argument with respect to the 857 and the large rearrangement analysis there as well. And, again, you can see the specifics of the allele to detect that alteration, to affirmatively detect it, literally required.

Same as here. I think it's time for a break, unless Your Honor has any questions.

THE COURT: I don't. Did you have in mind that we

would -- you had any examination of any witnesses on the infringement issues?

MR. GAEDE: So what we're going to do, Your Honor, is Dr. Roa has a few overlapping areas in here, but also that relate to the section 101 issue. So what Mr. Mangum and I agreed to is that at the conclusion of his 101 section, Dr. Roa would then take the stand, we would perform cross-examination that would go to both elements, and then we will go into our 101 presentation to you.

THE COURT: Great. Mr. Mangum, is there anything that you wanted to add very briefly by way of a response before we break or will it take more than five minutes if we open that --

MR. MANGUM: I think it will take more than five minutes.

THE COURT: I think so too. All right. Why don't we break. The lunch hour is approaching. Why don't we take about a 10 minute break and then try to go for about an hour or so until roughly 12:30, and then we'll break for lunch then so we can get another hour of argument in. We'll be in recess.

(RECESS FROM 11:21 am until 11:42 am)

THE COURT: Mr. Mangum, I think I regret my last question to you. I think we'll proceed without replies today so we'll get through what we have to get through. We'll leave

something for argument when we all come back. I understand your positions with respect to infringement, and of course I'll ask questions as we go if there are things that arise that I don't understand. But you'll have a chance to respond when we come back after we've received some post hearing briefing.

MR. MANGUM: Very well, Your Honor. The next module that we had intended to talk about was to head right into the section 101 issues with regard to the asserted claims and that they cover patent eligible subject matter. I've prepared a -- I'm kind of a visual guy, but I've prepared a slide that at least helps me. Perhaps it will help the Court.

It seems to me that really I want to talk about this slide because I think it presents the question that's in front of Your Honor, and then I'll go back with you through the Court's opinion and essentially build this continuum and discuss how it is that the Court sets up this continuum.

But the ultimate question, particularly with regard to the pair of primer claims with regard to section 101 in my mind, is we have a pair of primers that are synthesized and designed to work as a coordinated pair within PCR to amplify a target region of the BRCA1 or BRCA2 gene. Where does that lie in terms of its continuum that the Court has established with regard to patent eligibility?

And as I read -- and I'd like to walk through in some

detail with the Court the Supreme Court's decision. What the Supreme Court does is talks about -- and the law -- is about, well, we have products of nature, and we have things that are the result of human ingenuity or the product of the hand of man. And depending upon how close you are to the product of nature or how far down the continuum you are towards a product of human ingenuity determines whether or not something is patent eligible subject matter.

Now, in the AMP versus Myriad decision the Supreme Court -- that we'll walk through, the Supreme Court establishes essentially two points on that continuum. They say a human gene that's merely isolated from the body by breaking the covalent bonds, that's not enough of the hand of man to make that patent eligible.

Now, Judge Lourie of the Federal Circuit, along with one of his colleagues, thought that that was sufficient. Supreme Court said no, that's not sufficient, so that's ineligible. The Supreme Court then says, however, cDNA synthesized from mRNA, that is patent eligible. That's sufficiently down there. It does not occur naturally in nature. It involves synthesizing in the laboratory. That's sufficient.

So we have those two points on the continuum. And ultimately the question for this Court is where does this pair of primers that's synthesized and designed to coordinate and work together to amplify this target region, where does it

lie? And unless the Court concludes that it lies to the left of cDNA synthesized from mRNA, then it's an easy determination. Because we don't know -- there may be things that fit within this area between cDNA and the human gene that's only isolated by breaking covalent bonds that is nonetheless patent eligible, but the Court didn't reach that. But if it's further down towards the hand of man, not occurring in nature, product of human ingenuity, then -- I don't want to say it's a no brainer, but it's clearly then patent eligible, because if the court found cDNA synthesized from mRNA sufficiently involved human ingenuity to be eligible, then this must.

So let's go through with some detail the Court's decision. And the reason I think this is important -- and I know Your Honor I'm sure has poured over this decision like I have poured over this decision, and all of us have, is that largely what we have sometimes in the briefs and on both sides are characterizations of what the Supreme Court said rather than citations to what the Supreme Court said.

So I'm going to just limit myself here for the next five minutes as we go through, I'm going to go essentially page by page through the Court's decision and just look at what the Court said, not -- going to try not to characterize it.

So the court lays out here are the issues to be decided. This case requires us to resolve whether a naturally occurring

segment of DNA is patent eligible by virtue of its isolation from the rest of the human genome. Issue one.

Issue two. We also address the patent eligibility of synthetically created DNA known as complementary DNA, cDNA, which contains the same protein-coding information found in a segment of natural DNA but omits portions within the DNA segment that do not code for proteins.

So this next slide I just highlight a couple spots. The question: Is it patent eligible by virtue of its isolation? That's what the court was asking with regard to the genomic DNA. With regard to cDNA, is it eligible, since it's synthetically created in the lab, even though it contains the same protein coding information found in the segment of natural DNA?

So we have this dichotomy here about is it the information that makes it? Is it the molecules, the nucleotide sequence that makes something patentable or not patentable, or is it its source, its origin?

So here is their holding, and this is their brief holding right at the start, right after they state those issues. We hold that naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated.

And this actually in this slide is the same sentence. They then say, but that cDNA is patent eligible because it is

not naturally occurring. We, therefore, affirm in part and reverse in part the Federal Circuit. So key language there. Not patent eligible merely because it has been isolated. Patent eligible because it is not naturally occurring.

So back into the Court's decision. Here this -- again, there are back-to-back sentences within the Court's decision. What words do they use when they're describing the product of nature? What words do they use when they're talking about something that's the result of human ingenuity?

And I was working off the slip opinion. I don't know which version Your Honor has, but it's not a long opinion. It's fairly easy to find.

So a product of nature. Scientists can extract DNA from cells using well known laboratory methods. These methods allow scientists to isolate specific segments of DNA, for instance, a particular gene or part of a gene, which can then be further studied, manipulated or used. So when they're talking about genomic DNA, they're talking about extracting it to isolate it from specific segments of DNA.

Now, when they describe cDNA, or synthetic DNA, quote, it is also possible to create DNA synthetically through processes similarly well known in the field of genetics. One such method -- one such method begins with an mRNA molecule and uses the natural bonding properties of nucleotides to create a new synthetic DNA molecule. This synthetic DNA created in the

laboratory from mRNA is known as complementary DNA or cDNA.

The Court then recognizes the implications of its holding. What's going to happen if we rule one way on this issue or the other way on another issue? Myriad's patents -- this is the product of nature notion. Myriad's patents would, if valid, give it the exclusive right to isolate an individual's BRCA1 and BRCA2 genes, or any strand of 15 or more nucleotides within the genes, by breaking the covalent bonds that connect the DNA to the rest of the individual's genome. That's what happens, as I say, okay, those claims are patentable. With regard to the others, the patents would also give Myriad the exclusive right to synthetically create BRCA cDNA.

The Court then set up this -- these two issues. Now, what are the underlying policies that are to be applied to decide where something rests on this continuum? Product of nature. Laws of nature, natural phenomena, and abstract ideas are not patentable. Rather, they are the basic tools of scientific or technological work that lie beyond the domain of patent protection. Without this exception, there would be considerable danger that the grant of patents would tie up the use of such tools and thereby inhibit future innovation premised thereon. Continuation right in that same paragraph.

The rule against patents on naturally occurring things is not without limits, however, for all inventions at some level

embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas, and too broad an interpretaton of this exclusionary principle could eviscerate patent law.

So I think that discussion sets up that what we have here is a continuum not a dichotomy. It's not a hard and fast this is a product of nature and there's a clear dividing line between these things, because every invention involves at some level the application of natural laws or the use of naturally occurring materials that you then modify or apply in some particular way.

The Court then now says -- all right, went up to page 16, 17, 18 of the decision. There's two known points on this continuum. What is too much a product of nature to be patent eligible? Quote: We merely hold that genes and the information they encode are not patent eligible under section 101 simply because they have been isolated from the surrounding genetic material.

So, okay, Judge Lourie, you're wrong. Judge Moore, you're wrong. Just breaking covalent bonds isn't enough to make something patent eligible.

cDNA, the Court continues, does not present the same obstacles to patentability as naturally occurring, isolated DNA segments. Petitioners concede that cDNA differs from natural DNA but nevertheless argue that cDNA is not patent

eligible because, quote, the nucleotide sequence of cDNA is dictated by nature, not by the lab technician. That may be so, but the lab technician unquestionably creates something new when cDNA is made. As a result, cDNA is not a product of nature and is patent eligible under section 101, except insofar as very short series of DNA may have no intervening introns to remove when creating cDNA. In that situation, a short strand of cDNA may be indistinguishable from natural DNA. So two known points on the continuum.

Now I want to turn -- and I think this is -- this is the critical language of the Court's decision where both Defendants and their amici essentially try to drive a bus through this one clause. As a result, cDNA is not a product of nature and is patent eligible under section 101, except insofar as very short series of DNA may have no intervening introns to remove when creating cDNA. In that situation, a short strand of cDNA may be indistinguishable from natural DNA.

The question for you, what did the Supreme Court mean? What did it mean when it said that? Did it mean what Defendants and the amici say they meant? Let's get into exactly what was in front of the Court, what they said and what they didn't say.

This figure two is out of the Federal Circuit's decision in the Ambry versus Myriad case right before it goes up. So

what do we mean when we talk about short strands of DNA that don't have any intervening introns? Well, we're not talking about BRCA1 or BRCA2 because those are long and very complicated genes. They have very long exon regions. They have introns.

So when you take BRCA1 or BRCA2 and you, through the natural process to get to mRNA and then the synthetic process of getting cDNA, you end up with a sequence that does not exist in nature because you have removed -- the splicing has removed those intervening introns.

But not all genes are long and complicated like BRCA1 and BRCA2. Some genes consist of only one exon, so there are no introns that get removed in that process. And the Defendants admitted that and talked about that with you, and we both did, at the tutorial. This is from page 62 going over to 63 of the tutorial on the 23rd. In some circumstances, though, this is Mr. Gaede talking, you can make a cDNA that would be indistinguishable from the genomic DNA. So, for example, there are some where there just isn't an intron in between. And then they use this graphic to show that.

Well, that would be what you'd get with cDNA from a -- an mRNA or a DNA or a gene that does not have any introns. So not BRCA1, not BRCA2, not something that was before the Court, but that's what you would get. And that's what the Court was talking about. Well, maybe -- what's going to happen in that

circumstance?

So what did the Court mean? With genes consisting of only one exon and no introns, as we just talked about, the cDNA made from the mRNA will have the identical sequence as the original genomic DNA because there were no introns spliced out in the natural process whereby the mRNA was created. Such a circumstance was not before the court, the Supreme Court, therefore the Court need not and did not address that point -- I mean what the court says is clearly identified by it as dictum -- very short series of DNA may have no intervening introns to remove when creating cDNA.

So they're clearly talking about this natural transcription process that gets us down to the mRNA. So there may be some of those where you don't have any introns to remove. In that situation, a short strand of cDNA may be indistinguishable from natural DNA.

So why did the Court bother to talk about that if it wasn't in front of it? I mean it clearly identifies it as dictum. If you go back to the briefs before the Supreme Court, you get some enlightenment about why Justice Thomas either felt compelled or at least thought it -- at least that he should say something about this.

Here is -- this is taken directly from page 51 of AMP's brief. Although cDNA is frequently created in the laboratory using the above-described process, scientists have documented

the existence of the BRCA1 pseudogene1. And this is an issue that came up when Your Honor asked a question about it. A segment of the BRCA1 cDNA in the human genome. A ruling that DNA is not patentable because it is a product of nature necessarily would require a ruling that pseudogenes or cDNA are not patentable for the same reason.

So AMP's position before the Supreme Court was you should not only find that genomic DNA, something isolated by breaking the covalent bonds, is not patent eligible, but you should also find that cDNA is not patent eligible because of this anomaly or this phenomenon that can occur where you can have a segment of the BRCA1 cDNA in the human genome existing as a pseudogene, which as we talked about at the tutorial performs no function. It doesn't -- it doesn't have any coding information that can be used. It's essentially a defective piece that's sitting there.

So the Court addresses AMP's argument by that language we talked about, the except language, and specifically talks about it in footnote eight, which was a footnote that when I read it I went what in the world. They go to footnote eight and they hold there that the possibility of there being a synthetic molecule -- the possibility that there's a synthetic molecule that's similar to one found in nature does not affect patentability. And here is the first half of footnote eight and the next slide has the next half.

Some viruses rely on an enzyme called reverse transcriptase to reproduce by copying RNA into cDNA. In rare instances a side effect of a viral infection of a cell can be the random incorporation of fragments of the resulting cDNA, known as a pseudogene, into the genome. Exactly what was talked about in the brief.

Such pseudogenes serve no purpose. They are not expressed in protein creation because they lack genetic sequences to direct protein expression. That footnote continues. Perhaps not surprisingly, given the pseudogenes' apparently random origins, AMP has failed to demonstrate that the pseudogene consists of the same sequence as the BRCA1 cDNA.

And then here is the holding language. The possibility that an unusual or rare phenomenon might randomly create a molecule similar to one created synthetically through human ingenuity does not render a composition of matter nonpatentable.

So what did the court mean? I think we have now some context for what the court was talking about. Specifically is saying this issue is not in front of me because BRCA1 and BRCA2 are long and complicated genes and so I don't have to look at this notion that, well, boy, in some instance you could have a cDNA that's identical to the genomic DNA. And they reject this notion that the fact that there might be

something out there floating in space within somebody's body that matches up with a synthetically created molecule just isn't important. It does not render that nonpatentable.

So, thus, AMP argued that cDNA should be found unpatentable because it was possible that a similar naturally occurring molecule, i.e., an exon-only segment of the BRCA1 or BRCA2 gene, existed within the body in the form of a pseudogene.

Nonetheless, the court held that this mere possibility was insufficient to render cDNA, and by extension other molecules created synthetically through human ingenuity, unpatentable.

So we're back to our continuum. Where does this pair of primers synthesized and designed as a coordinated pair to amplify in PCR a target region for the BRCA1 and BRCA2 gene? That's what the court tells us and that's what we then go on to address.

So I think what's important here, Your Honor, is we have picked very narrow claims, very narrowly defined claims to assert in this case. So while I've told you what my view is of this continuum, the Court does not need to go so far as to hold that all synthetic DNA is patent eligible, although I think the Supreme Court's decision supports that. You don't have to go that far to enter an injunction in this case and find that we have a likelihood of success on the merits

because the primer pairs at issue here are clearly patent eligible under AMP.

So let's look at those factors that the Court talked about. We have a pair of single-stranded DNA primers. They're designed to work in conjunction with each other in a PCR chemical reaction to prime the artificial synthesis of a new molecule having a portion of the BRCA1 and BRCA2 sequence. That does not exist anywhere in nature.

You don't have a -- first of all, you don't have DNA primers that exist in nature. You don't have a pair of them that are specifically designed because the design requires the human ingenuity. They're designed to work in conjunction with each other to prime this PCR chemical reaction. PCR cannot -- does not occur in the body. It does not occur in nature. And you create a new molecule. You create these amplicons that we talked about at various times during the tutorial and otherwise that have a portion of the BRCA1 and BRCA2 sequence that don't exist in that form in nature.

And I submit to you, Your Honor, that when we think back about that continuum, that, the pair of primers, involves much more of the human ingenuity than does taking a naturally occurring mRNA and through a process convert that to cDNA in the laboratory synthetically.

And since the Supreme Court found that taking mRNA and making cDNA out of it was patent eligible because it involved

enough human ingenuity, you know, these pair of primers is far down that continuum from cDNA.

So here -- this summarizes our points about why we believe that the primer pairs are patent eligible under AMP. They're synthetically created in the laboratory. They're not extracted from the body. So when we get back to the Supreme Court's decision where it talks about extracting something by isolating it from the body versus synthetically created -- and Dr. Pribnow acknowledges that in his declaration, that primers, primer pairs, are synthetically created in the laboratory. They're not extracted.

Point two, no comparable element exists in nature. A matched pair of single-stranded DNA molecules that hybridize to preslected ends of the target region on the BRCA1 or the BRCA2 gene. It does not exist in nature. The primers are carefully designed and defined by scientists, often after significant optimization through trial and error.

So they sit there and look at that BRCA1 and BRCA2 sequence and try to figure out, as we talked about in the tutorial, well, where is there not a lot of duplication? Where is there a region that doesn't vary a lot between different individuals so that I can get a targeted and efficient amplification? So, thus, involves much more of the hand of man than cDNA made from mRNA.

And this chart just kind of summarizes that. A pair of

primers designed to prime a PCR reaction involves much more of the hand of man than cDNA from BRCA mRNA. Just side by side think about that. BRCA cDNA, you take a naturally occurring mRNA that's extracted from a cell and you use that as the starting point. So right up until the time that you go to the lab and you start to make your cDNA, it's all a natural -- naturally occurring process.

In contrast, a synthesized specific -- BRCA specific primer pair is synthesized from scratch with no starting material extracted from the cell. Yes, you need to know -- you're using knowledge about what the BRCA1 and BRCA2 sequence is like so that you're using knowledge that comes from nature, but what you're making and what you're designing is synthesized by you from scratch based upon your decision or the scientist's decision about what's going to be an efficient pair of primers to achieve this.

BRCA cDNA. It contains the same protein coating information found in the segment of natural DNA -- undisputed. That's what the Supreme Court talks about. Petitioners say that, well, it can't be patentable because the technician's not deciding the sequence. That's dictated by nature. The Court says that's not -- but that's what's true with BRCA cDNA.

Think about it over here with a primer pair. Those primers do not code for a protein. They don't perform any

comparable biological function as a segment of natural DNA while the cDNA codes for proteins the same way that the exon regions of the genomic DNA would.

That's not true of the primers. They don't code for a protein. They're the equivalent of a tool. You know, you have formed a tool, synthesized it, and now you're using that tool that you designed to perform a function that doesn't exist in nature, PCR, that then amplifies the target regions that you've dictated. And I submit that's much more human ingenuity, much more the hand of man than cDNA.

And this is a slide -- it's a slide, I think it's 46, from Defendants' tutorial, which just shows the process by which cDNA is made. And it just emphasizes the fact that the only thing that involves work in the laboratory is just that last step as contrasted to what we're talking about with primer pairs.

So the claimed primer pairs are patent eligible -- this is an additional reason -- because they are distinct from naturally occurring DNA. In the case law in this area, a lot of the discussion is through the process that you're applying, do you create a distinct molecule, something that is distinct from something that's naturally occurring?

So that's true here with regard to these primer pairs. A pair of relatively short molecules with different chemical structure and function than anything that exists in nature.

So it's distinct from the naturally occurring DNA. It's different -- so it's different in structure. It's different in terms of the range of uses that it can be put to. It's capable of catalyzing a chemical reaction to synthesize a specific DNA molecule of interest. And used in -- it's used in PCR, a process that has no analog in nature.

And those two things, I mean particularly that second, that's something that cDNA cannot do. I mean cDNA cannot catalyze a chemical reaction. It can't be used in PCR. And yet cDNA, even though what it does is the same thing that the naturally occurring molecule does, which is code for a protein, is explicitly found patentable by the Supreme Court.

So, Your Honor, we've now covered the primer pair, the -- the composition of matter claims and now I'm going to turn to the method claims and discuss why those are also eligible under AMP and Mayo.

THE COURT: Thank you.

MR. MANGUM: I think one thing that's really important to look at at the outset is that it's important to remember that the AMP versus Myriad case is the -- is a case that is returning to the Supreme Court after it has been remanded for reconsideration in light of Mayo. Am I making myself clear about that?

The Myriad case, it gets -- certiorari is granted in the Supreme Court. In the interim the Court has issued their Mayo

decision and they say, okay, Federal Circuit, take another look at this now that we've looked at Mayo, now that we've rendered the decision in Mayo. The Court does that. The Federal Circuit comes to essentially the same conclusion it did before Mayo and it comes back up to the court.

So the Supreme Court's acutely aware of its Mayo decision, immediately prior term, when it's looking at AMP versus Myriad. And I think that's significant because if we now look at -- and, again, not characterization but citation -- the Court's statements in AMP regarding method claims and Myriad's ability to patent methods of applying its discoveries, those comments by the Supreme Court make absolutely no sense if Defendants' view of the Mayo decision are correct. If Mayo totally wipes out any notion of there being method claims like the ones that are asserted here, you know, why would the Supreme Court have gone out of its way to say here is not what's in front of us, and do more than that. Let me show you exactly what they said, again, citation not characterization.

So the Court, AMP Court, emphasizes the narrowness of its holding and that it did not affect Myriad's claims. They say it is important to note what is not implicated by this decision. First, there are no method claims before this court. Similarly, this -- and this is, again, the next sentence from the Court. Similarly, this case does not

involve patents on new applications of knowledge about the BRCA1 and BRCA2 genes.

Then they cite with approval what Judge Bryson said below. Judge Bryson aptly noted that, quote, as the first party with knowledge of the BRCA1 and BRCA2 sequences, Myriad was in an excellent position to claim applications of that knowledge. Many of its unchallenged claims are limited to such applications.

What we submit to Your Honor is that the method claims that we're talking about here fit exactly into this area. They are applications of knowledge from the discovery that Myriad made of the sequence of the BRCA1 and BRCA2.

THE COURT: Of course Judge Bryson goes on in his opinion to recite three specific claims in three specific patents.

MR. MANGUM: He does.

THE COURT: So do we compare those with these to get some idea for whether this is the kind of claim that Judge Bryson had in mind?

MR. MANGUM: I think we -- I do. I think we have to look at the specific claims that we are asserting, and particularly the notion that comes out of Mayo -- and I'm about to launch in and talk to you about Mayo -- that are the claims that -- the method claims that are asserted by Myriad here, are they mere mental abstraction application steps or

are there discrete, transformative tests types -- type tests.

But I think that's a very fair analysis to do, to compare how these claims that we've asserted, these method claims, match up to what was found insufficient in Mayo and what was found, some of them, insufficient by the Federal Circuit in terms of Myriad claims, what were found sufficient.

And then there's another important case in this, and that's the Diehr case from the Supreme Court, Diamond versus Diehr because that -- you know, unlike some of the other cases, that's a method case, method claim. And if you look at Diamond versus Diehr, it talks about how method claims in particular should be viewed. And I don't think Diamond versus Diehr is cited in either of the briefs, but there are some great -- there's some very pertinent language in Diamond versus Diehr that I'll see if I can direct the Court's attention to here.

THE COURT: That's a Federal Circuit decision; right?

MR. MANGUM: No, it's a Supreme Court, Your Honor. It's -- the cite on that is 450 U.S. 175, 101 Supreme Court 1048, if that's an easier one, Diamond versus Diehr. Diamond, of course, at that time, the Commissioner of Patents, 1981 Supreme Court decision.

And I'll just point out to the Court, you know, they're dealing with method claims. It's an interesting -- it's a

method claim for galvanizing rubber. And the whole issue that's before the court is that there's an equation out there that says how long you should cure rubber for -- you know, how long you should heat it up to get what you want, what temperature and everything else. And so you're applying this natural equation. And there's a method that's designed and patented that talks about how to specifically apply that.

And what justice Renquist says, speaking for the Court, he says, it is now commonplace that an application of the law of nature or mathematical formula to a known structure or process may well be deserving of patent protection. So particularly with regard to method claims, I think Diamond versus Diehr is a very important authority for the Court to look at along with Mayo.

So let's talk about Mayo, how Mayo and Myriad are different. On the left side here it's talking about Mayo. It's important to recognize that everything that was in Mayo's claim was known and in use at the time of the filing of that patent application. Okay. The drug that it's talking about -- I have it on another slide and I won't be able -- I'm probably not able to pronounce it even when I read it off the slide let alone from memory.

But there was a known drug metabolite that was used as a known biomarker. That was known prior to the time that Prometheus filed its patent application. Second, the

association of that biomarker to a particular clinical characteristic was known, well known. Third, the assay techniques, so the extent they had any methodologies for that specific biomarker were known. So it's -- it's not -- not equivalent to saying, well, PCR was known. It's that that -- the assay techniques that were specifically used for that biomarker were already known. So you already had the information that you needed to be able to do the specific technique.

So what did the patentee offer? All the patentee did was refined a previously known therapeutic range and instructed the physician about the relevant natural laws. You give the person this drug. You then test for it in their body. If it's too low, what do you do? You give them more. If it's too high, you cut down on the dosage. So all of that was known, and all they did was they -- there was a therapeutic range before that was this broad, and after Prometheus they said, well, let's put it here.

So how is that different from the situation in Myriad? At the time that patent applications are filed, the -- we're talking about now a previously unknown biomarker, the BRCA1 and BRCA2 genes. There were people out there looking for them, but they didn't know where it was or what its sequence was. That biomarker was not known at the time that Myriad filed its patent applications.

There is a new clinical indication, unlike before where there was already known that there was this association. They're now -- we know that this sequence and different variants of that and mutations within it have -- are clinically indicative of hereditary breast and ovarian cancer, not known before the patent claims were filed, known afterwards.

And then you have specific applications of these generalized techniques, like PCR and sequencing, to develop new assays for the new biomarker. So, yes, I mean I'll concede immediately PCR was known, sequencing was known, but what's claimed in these patents isn't PCR and sequencing. It's performing PCR using these specific designed pair of primers to target a specific region of the BRCA1 or BRCA2 gene and then sequencing that. So that's the difference with regard to that.

Other differences. There are more differences between these two cases than you can fit on one slide. Mayo, these differences look about -- about the differences in the claims that were in these two cases. In Mayo what you had were claims to, quote, administering and determining steps that are articulated at a very high level of generality. And essentially I think it was Justice Stevens that said -- maybe not Stevens -- abstract suggestion that the physician take into account these relevant natural laws when it's treating

the patient. So abstract high level of generality steps not specific steps.

In Myriad, our method claims, the claims are directed to specific application of techniques, amplifying, sequencing, probing by hybridization and screening that are specifically tied and directed to this newly discovered -- these newly discovered biomarkers, the BRCA genes. The claimed applications and attendant primers, probes and amplicons didn't exist before. They were unknown, and indeed they were really, as a practical matter, impossible to know until the gene sequences were known.

So here are some sample claims between these two cases. Under Mayo, step, administering a drug providing 6-thioguanine to a subject, and then determining the level of that same drug in the subject. That was their claim. Have them take the pill, shot, check their body, see how much is there, and then make some decisions based upon that.

In contrast, claim seven in the 441 patent, hybridizing a BRCA1 gene probe which specifically hybridizes to a BRCA1 allele. So it's tied into that very specific new discovery, so like the Diehr case, applications of knowledge of this newly discovered information.

Claim eight of the 441 patent, amplifying all or part of the BRCA1 gene from said sample. So not administering and determining. And the other thing, I think, just to be fair,

there are certain of our claims that have elements of those method claims, that have some of these comparison type steps, but the important thing is that it doesn't only have that. If we had a claim that just said do this and then compare, you know -- strike that. If we had a claim that said compare the sequence of the patient's BRCA1 gene to the sequence of the wild-type, that wouldn't be patentable under Mayo. But we don't have those types of claims. We have those steps plus some very specific application steps that distinguish us from the Mayo situation and put us more in line with the Diehr and other cases.

So Mayo. Here is the claim language. Determining the level of 6-thioguanine in said subject. Contrast Myriad. Claims recite specific chemical assays that were, importantly, not routine at the time the patents were filed. In Mayo the procedures that we're talking about were already known and routine, specific procedures tied to that specific drug and biomarker, not true with regard to Myriad.

Indeed, the specific assays that we're talking about with Myriad's claims were impossible as a practical matter without prior knowledge of the BRCA1 and BRCA2 sequences. So asserted method claims are patent eligible under AMP and Mayo.

And this really overlaps a little bit with what we'll talk about later when we get to the obviousness and things. Just bear with me on that. Defendants cannot properly

attempt -- attempt to use Myriad's own discovery of the BRCA1 and BRCA2 gene sequences to invalidate its method claims. The proper question is whether Myriad's specific claimed methods were routine, conventional activity previously engaged in by scientists before the patent was filed, not whether, having the benefit of Myriad's landmark discovery, one of skill would know how to develop such methods.

That's the difference. When you're looking at patent eligibility and you're looking at this, you're not -- you don't get to say, well, once we had this discovery, would somebody else have been able to do what you came up with? Or, you know, if we waited long enough would somebody else have come up with that?

And I think this is probably the final point. Otherwise, if that were the law, the Supreme Court's statements in AMP regarding Myriad's ability to patent methods of applying its discoveries regarding the BRCA1 and BRCA2 genes would make no sense. I mean the Court was fully aware of Mayo. Why would they have made those gratuitous statements if they thought that it's -- their own decision in Mayo has wiped out any ability to claim that. And that would have been contrary to their own precedent in Diamond versus Diehr.

So it's important to note -- and this is the language that I started with From the Court. It's important to note what is not implicated by this decision. There are no method

claims before the court. Similarly, this case does not involve patents on new applications of knowledge about the BRCA1 and BRCA2 genes. That's what's at issue in this case, applications on method claims, applications of the knowledge of BRCA1 and BRCA2.

One additional ground why the method claims are eligible, patent eligible. They're eligible in and of themselves, but they're also eligible for the additional reason and independent reason that those method claims incorporate the use of the primer pairs, the novel patentable compositions of matter, the primer pairs, the amplicons and the probes that I addressed previously. And that comes right out of the Federal Circuit's decision in AMP on remand.

And this is what the Court says. Once one has determined that a claimed composition of matter is patent eligible subject matter, applying various known types of procedures to it is not merely applying conventional steps to a law of nature.

THE COURT: Is the converse true also?

MR. MANGUM: No, because what I said before is the method claims can be patent eligible independently, but if you find -- if you find that the composition of matter is independently, then a method applying that carries that over but the inverse is not -- is not.

With that, Your Honor, unless there's some specific

questions or areas, I certainly have additional materials with regard to this. And I guess what I'd indicate is I possibly want to go through some of those additional materials if you're not going to contemplate rebuttal on the presentation with regard to the 101 issues.

THE COURT: Well, I'll hear whatever you want to present today. We're here for the purpose of creating a record, but we'll be back for final argument after you've had a chance to digest conclusions and findings. But if there's something more you think is relevant today -- I also understand that notwithstanding the volume of the briefing, we've very carefully digested it and all the case law. But this is helpful. It's a helpful exercise for the Court, and it's your opportunity.

MR. MANGUM: One thing that I think is -- maybe two or three slides that I just want to address.

The Court: Of course.

MR. MANGUM: I want to drop back now and just talk about what -- what does -- what would -- if Defendants' view of the law were adopted, what mischief would that cause in terms of what would not be patent eligible out there.

THE COURT: I'd actually like to talk about the forest a little bit today and not just the trees. I've got a really close look at the trees in your briefs, and I'm interested in your -- relatively, both of you, your

perspectives on the forest.

MR. MANGUM: Okay. And this ties back into in some respects the chain analogy that we talked about during the tutorial. And the point I want to make -- and I just want to give you a couple of examples. How dramatic -- you know, we talk about A, C, D, G, but the concept is we're talking about a chemical compound, and we're talking about chemical molecules and how dramatically different a chemical molecule is once it's extracted or once even one little link is removed. And I want to just give you a couple of examples of that.

Here, as you'll see depicted, there's two chemical compounds, the only difference of which is that there's this little called a hydroxyl life, now I understand, that's a link that's down there on that -- on that one spot. The other one doesn't have it.

So here we have an example. We have the naturally occurring nucleoside that's converted to an active therapeutic drug by that hydroxyl being eliminated. So it's not -- so you could do it by taking that off or you could do it by synthesizing the molecule without that on it.

So the compound on the left, it's name is there. That's as far as I'm going to go. It's found naturally in the DNA of a virus, okay? Exists in nature. That same compound removed the hydroxyl from the three prime location, or synthesized

that same molecule and omit the hydroxyl from that location, an entirely different molecule.

And while I won't pronounce the name, I will point out to you that you'll notice it's a dideoxy. You'll recall from the tutorial that that's -- that's that nucleotide that stops -- stops the reaction, stops something from replicating itself, dideoxynucleotide.

So it's the same as the DNA from that virus, but it's missing the hydroxyl group from the three prime. What happens? That is a drug, Amdoxovir, an HIV drug. It is a patented composition of matter, and its only difference is that one molecule.

So how does that drug work? And this goes back to what we talked about during the tutorial. By removing that hydroxyl and making this into a dideoxynucleotide, that drug inhibits the replication of the virus. So it's that same principle that would stop a PCR reaction where you wanted it to stop that applies in the human body to stop an HIV virus from going wild and replicating itself.

So the natural compound is used by the -- so the virus we talked about, the left side, is a natural compound that's used by the virus to hijack the cell operations, and it forces the cell essentially to make copies of itself. That's what it does in nature. You take the dideoxy version of that natural compound, this drug, and it causes a termination of that DNA

synthesis and therefore is retardant to the progression of HIV.

SO what would happen if the Court were to go, or the law were to go -- the law were to go to the point where these types of submolecules are not patentable? So a submolecule of a naturally occurring larger molecule in this example gains dramatic new utility by the simple act of removal of the one hydroxyl group, the removal of one of the chains essentially for your analogy.

So you looked at -- think back about that picture we had up in front of you. If you look at the left side, can you see the molecule that's on the right side within that? Yeah, you see it. It's the same thing without that on there. So the mere fact that you can look at it, look at that chain and say, well, here's the 10 foot chain, but I can see that one foot chain there in the middle of that 10 foot chain. That has dramatic consequences within it.

Now, you can see the difference between those two molecules a lot quicker than you can see the difference between a primer pair or an individual primer for that matter that's 15 to 30 nucleotides versus the 81,000,000 plus nucleotides that are on chromosome 17 or a one foot segment can be seen within a 10 foot chain.

So Amdoxovir, by missing one small chemical group from the naturally occurring DNA, once you synthesize that, missing

that in part, it functions entirely different. Same thing occurs. Its analogous to the BRCA1 specific primers. They're missing more than 81,000,000 nucleotides from chromosome 17, and they're missing at least 100,000 nucleotides from the genomic BRCA1. But because of that, they perform -- they perform none of the functions -- and this is critical I think. That primer performs -- the pair of primers perform none of the functions that that sequence does when it's within that bigger chain. Within that bigger chain, if you know exactly where to read the codons, each of those three pair, you know, that combination of three, is going to express an amino acid and develop protein. Primer pairs don't do that. They don't code for the proteins. They perform an entirely different function. They prime the PCR, targeted PCR amplification that does not occur in nature.

Let me give you one more example because I thought this was kind of cute. What can Gusperimus teach us about chains? So here we have again two molecules, one, the top one, an antibiotic isolated from Bacillus laterosporus. Below it the exact same molecule, except that one, again, Hydroxyl group is missing from that one link. So it's the same thing, and it's Spergualin with just one hydroxyl group removed. And it's an immunosuppresive drug that can be used for a variety of hyperreactive inflammatory diseases such as autoimmune diseases, and it's patented.

So now we take it back to that multicolored chain. We take one of those links off. We can see the smaller segment within the larger one, just one link has been removed, yet the molecule has a new, expanded range of utilities. And that's one of the things that the case law really points out. You make a change such that the new molecule has an expanded range of utilities that the old molecule did not. That's talked about in Funk Bros. It's talked about in Chakrabarty.

So the analogy in my mind is clear. You know, when you make these pair of primers, you haven't just removed a side link from a small chain, which is what the scientists did was design an entirely new pair of small chains which happen to share some links with the larger natural chain, and together they have new and expanded range of utilities, namely priming this PCR reaction.

The COURT: Would you say in the language of Funk Bros. and Chakrabarty, would you say that the two examples you've just provided to us -- I'm looking for the specific language. Do they have markedly different structures without the single molecule in both instances? They have, you've convinced me, different utility. Do they have markedly different structures?

MR. MANGUM: Well, I think the question there, as a chemical compound, yeah, because that -- that one -- you know, I'll use terms that I think you and I as nonscientists -- that

one little difference -- so if you looked at it from a standpoint of saying, well, those two pictures, are they markedly different? Well, is the removal of just one little thing markedly different? I mean it would be much easier to say that the difference between the primer pair is markedly different than that full sequence of the gene or even an amplicon.

But even with these things, I think the point of all this is when you're talking about chemical compounds of what visually would look like a very small change has a dramatic effect on that chemical compound, that chemical -- not just its functions but the chemical compound itself can look entirely different the way it would, you know, spin up or work or anything else.

The Court: Well, do you think that Judge Bryson has it right when in his portion of his -- of that appellate decision he says that we should view -- I think he's talking just specifically about Chakrabarty, but I think this is also true in Funk Bros., or could be, that we have to look separately at whether there's a significant difference both in structure and purpose. And does your answer to my last question collapse those two?

MR. MANGUM: I don't think so. I mean I'm not a chemist, but my -- what I am concerned about in terms of -- you know, is that from a chemical standpoint, would we look at

a model of a molecule and we say, well, this thing is taken off from it? If we look at it as an economics major, we look at it and say, well, boy, you know, it's not very different. That's just one thing over there is gone. Or if we look at the chain analogy, well, you know, I had this 10 foot chain but now I can see this one foot in here and -- but I think when you then translate that to say we're not talking about a model and we're not talking about a chain, we're talking about a chemical compound. Apart from the fact that it's function may be significantly different, its structure to a chemist and the way it would look in nature, you know, if you could see it, the model -- I guess the point is the model or the chart is an abstraction of what that molecule really is.

And I believe for purposes of what Judge Bryson is talking about, the appropriate thing to do would be look at the difference of that molecule in terms of its structure and independently its application. And its structure, even though to me or to a common looker may look very similar, it wouldn't to a chemist.

And I guess kind of take that to the next step. It's interesting, Judge Lourie, who wrote the opinion, is a chemist. He's a patent lawyer and a chemist. Judge Bryson was a lawyer in the Justice Department. So I can't answer your question from a chemical standpoint, but I don't think I'm collapsing the two together.

The COURT: And I think it was Judge Bryson who suggested that maybe it was the view of a geneticist, which is the right lens through which to look at this, but I gather the response would be the same. You flip a G and a C for an A and a T in a sequence and you can have a profound difference. You're going to build a different amino acid. You're going to build a different protein. So it may seem minute in structure, the difference, but the ramifications are profound.

MR. MANGUM: Absolutely. And I don't know if it would be helpful, Your Honor. I did anticipate that there -- I'm prepared to kind of walk you through Funk Bros. and Chakrabarty and those things, but --

The Court: You can't imagine how much time I've spent reading them. I think I understand.

MR. MANGUM: All right. With that, Your Honor, I submit this issue.

THE COURT: All right, thank you. I think this is probably a good time to break for lunch and give everyone a chance to eat and breathe rather than to break up your presentation, Mr. Gaede.

Normally with lawyers I -- we just come back and start sooner rather than later. I think there's a lot of people with interest here and a lot of people that probably have some things to do, so let's take a full hour. Let's plan to come back and resume at quarter to 2:00, and we'll get a good bit

more water under the bridge today. We'll be in recess.

(RECESS FROM 12:46 pm Until 1:53 pm)

THE COURT: All right. We'll go back on the record. Mr. Mangum, hi. There you are again.

MR. MANGUM: Thank you, Your Honor. The next step is we'll be putting Dr. Roa on the stand. But to follow up with one question from the Court, having the lunch hour, we couldn't resist one more slide. That's that comparison that you had asked for, and that's a comparison between one of the specifically identified unchallenged claims from Judge Bryson comparing that to one of the claims at issue here. And as you see, they match up essentially.

One is talking about RNA, one is talking about genomic DNA isolated in terms of the method claim hybridizing step, detecting step, so that there is a nice correspondence between those types of claims and claims that are asserted here.

With that, Your Honor, we'd call Dr. Benjamin Roa to the stand.

THE COURT: Thank you. Dr. Roa, come forward, if you would, please, and be sworn.

MR. MANGUM: And Mr. Jackson of our team will be doing the examination just to put him on and lay the foundation for his declaration.

THE COURT: We'd be happy to hear from him.

MR. MANGUM: Thank you.

The CLERK: Please raise your right hand.

(BENJAMIN ROA, PLAINTIFFS' WITNESS, SWORN)

Thank you. Please be seated. Please state and spell your name for the record.

THE WITNESS: Benjamin Roa, B-E-N-J-A-M-I-N, R-O-A.

THE COURT: Please.

DIRECT EXAMINATION

BY MR. JACKSON:

Q Thank you. Dr. Roa, if you could just again please state your name for the record.

A My name is Benjamin Roa.

Q Okay. And who are you employed by?

A I'm employed by Myriad Genetic Llaboratories.

Q And what is your title at Myriad?

A My title is Vice President for Technology Development and Laboratory Director.

Q Okay. In general terms, what are your duties at Myriad?

A So I oversee a group that does development of new tests for the clinical labs, and I also will receive the clinical reporting of our tests.

Q Thank you. Could you please give the Court a general overview of your academic credentials.

A So I obtained my Ph.D. in molecular biology from Northwestern University. And I did postdoctoral training in

molecular and human genetics at Baylor College of Medicine, and I'm also Board Certified by the American Board of Medical Genetics in clinical molecular genetics.

Q Thank you. Have you prepared and submitted a declaration in this case?

A Yes, I have.

Q Let me hand you a copy of that declaration.

Your Honor, may I approach?

THE COURT: Please.

MR. JACKSON: I'll also hand a copy to the Court and to opposing counsel.

THE COURT: Thank you.

Q (BY MR. JACKSON) So is this a copy of the declaration that you submitted in this case?

A Yes.

Q Do you understand that this declaration is the equivalent of sworn testimony in the case?

A Yes.

Q Is that your signature on page 18 of the declaration?

A Yes.

Q And did you in fact sign that declaration on July 9th, 2013?

A Yes.

Q When you signed that declaration, did you understand you were attesting to information contained in the document under

penalty of perjury?

A Yes.

Q Have you reviewed your declaration recently?

A I have.

Q Did you see anything in your declaration that you feel requires correction or clarification?

A No.

Q Would your testimony today be any different than what is set forth in this declaration of July 9th?

A No.

Q Do you adopt your declaration as your testimony to the Court?

A Yes.

MR. JACKSON: Thank you, Dr. Roa.

Your Honor, we pass the witness.

THE COURT: Mr. Gaede.

CROSS-EXAMINATION

BY MR. GAEDE:

Q Good afternoon, Dr. Roa.

A Good afternoon.

Q If I can move this and get set up in a way that might help us.

Good afternoon, sir. You recognize your declaration also on the screen there?

A Yes.

Q Okay. It might be easier if we could all look at that together. First of all, let's make sure on one point here that we're in agreement on. Now, here in paragraph 12 of your declaration you state that BRCA1 and BRCA2 are the names of two genes that can provide information relating to a patient's susceptibility to develop breast or ovarian cancer. Do you see that?

A Yes.

Q And so you agree that the BRCA1 and BRCA2 genes do provide information relating to a patient's susceptibility to developing breast or ovarian cancer; correct?

A Yes.

Q And that that information is contained in the sequence of the BRCA1 or BRCA2 gene; correct?

A Yes.

Q So we agree that DNA can contain information; correct?

A Yes.

Q All right. Now, this is a schematic that you put into your declaration, correct, for the Court?

A Yes.

Q And here what you're showing is two primers; correct?

A Correct.

Q And we can agree that the sequence that is displayed in the forward primer is the exact same sequence as is set forth in the three prime to five prime strand, that portion of it;

correct?

A For the forward primer --

Q I'm sorry, five prime to three prime I mean.

A Yes.

Q Sorry, my mistake. And that the reverse primer on the five prime to three prime also contains the exact sequence that's predicted shown on the lower part from five prime to three prime; correct?

A Yes.

Q Okay. And so the sequence that is there is exactly the same as a portion of the larger sequence that is depicted; correct?

A The portion of that sequence, yes.

Q Okay. Now, is that what you call in this case where every nucleotide has a complement to the sequence on the opposing strand precisely complementary?

A Yes.

Q Okay. So when you use the word precisely complementary in your declaration, you mean that every nucleotide will bond -- in that primer will bond by Watson-Crick base pairing to the opposing strand; correct?

A Yes.

Q Okay. And so when you write in your declaration at paragraph 16, quote, primers are specifically engineered with a laboratory-designed sequence of nucleotides that is

precisely complementary to a region of a single strand of the target DNA to be sequenced, such as the BRCA1 region of chromosome 17q and/or the BRCA2 region of chromosome 13, or more typically a small portion of one of those genes, such as the tiled amplicons shown in figure three, what you mean by that is a primer will have a complementary nucleotide in the BRCA sequence; correct?

A Yes.

Q Okay. And all nucleotides in the primer will have that complementary to the opposing sequence in the BRCA2 or BRCA1 sequence; correct?

A As depicted in this diagram, yes.

Q And as stated in your declaration, that such as for the BRCA1 region of chromosome 17q, the primer will be precisely complementary; correct?

A Yes.

Q Okay. So precise complementarity is dictated by the BRCA1 sequence or the BRCA2 sequence; correct?

A Correct.

Q All right. And of course the BRCA1 and BRCA2 sequence is naturally occurring; correct?

A The sequence is, yes.

Q Of course. I mean Myriad didn't make the gene; correct?

A Correct.

Q The sequence has been around for millions of years likely; correct?
A Correct.
Q Okay. So all Myriad did was to identify that sequence that already existed in nature of the BRCA1 and BRCA2 gene; correct?
A Myriad made the association and with hereditary breast and ovarian cancer with this specific gene sequence.
Q With the specific gene sequence but not the fact that BRCA1 was potentially involved in causing breast cancer; correct?
A That's what I mean by the association with breast cancer.
Q So you're saying that before Myriad discovered the BRCA1 actual gene sequence, it was unknown that there was an association between BRCA1 mutations and breast cancer?
A Yes.
Q You're saying that?
A Yes. The discovery of the gene was this is the gene sequence for BRCA1 wherein mutations are associated with hereditary breast cancer risk.
Q You, of course, have read the patents in the suit?
A I'm sorry?
Q You've read the patents that Myriad is asserting against --

A Some of them, yes, not all of them.
Q You recognize that a lot of the patents have a common specification?
A I'm not a patent lawyer. I can't really say.
Q You don't know?
A I don't know.
Q Have you read the 282 patent?
A I'm not sure.
Q Okay. Well, let's take a look. It's already in the record.
Your Honor, would you like a copy of it or would you like to see what's on the screen?
THE COURT: Either is fine.
MR. GAEDE: You already have a copy of it.
THE COURT: I'm sure I could use more paper.
Q (BY MR. GAEDE) We've marked this, your copy, Doctor, as Defendants' Exhibit 1. Do you recognize Exhibit 1?
A I have to say I have not specifically reviewed this patent in preparation for my testimony today.
Q Have you reviewed the patent in the past?
A I don't recall.
Q You don't recall? Okay. You see the term background of the invention?
A Yes.
Q Do you see that where it says right here at column two,

breast -- at line 55, 56, quote, breast cancer has been subdivided into two types, early-age onset and late-age onset based on an inflection in the age-specific incidence curve around age 50, period. Do you see that?

A Not from where I'm sitting, I'm sorry. Which page would that be?

Q If you look at -- let me --

May I approach the witness, Your Honor?

THE COURT: Please do.

MR. GAEDE: Thank you. Help him get there faster.

Q (BY MR. GAEDE) Background of the invention, column two, we're right there.

A Okay.

Q Okay? Do you have that before you, sir?

A Yes.

Q Okay. So here in the background of the invention, Myriad and the other parties that are associated with this patent represent, quote, mutation of one gene, BRCA1, is thought to account for approximately 45 percent of familial breast cancer, but at least 80 percent of families with both breast and ovarian cancer, citing to Easton in 1993. Do you see that?

A Yes.

Q Okay. So it was known prior to Myriad isolating the sequence of the BRCA1 gene that mutations in the gene were

thought to be an approximate 45 percent of familial breast cancer causes; correct?

A That's what it says.

Q Okay. And so it was known prior to Myriad isolating the gene that mutations in that gene had a role in breast cancer; correct?

A It was known that there was a gene, but it was not known what exactly or where exactly that gene was.

Q Okay. But it was known there are mutations, correct, in that gene?

A It was assumed to have mutations, yes.

Q Now, let's go back to your declaration, and specifically if we could go to paragraph nine of your declaration.

A Yes.

Q And here you talk about the broader sequence of the gene being created by nature, and that the primer is defining the boundaries, the beginning and the end points, of the sequence to be amplified; is that right?

A Yes.

Q And we can agree that using a primer that is precisely complementary to the BRCA1 sequence, two primers, it will make an exact copy of that genomic sequence; correct?

A It will make an exact copy of the sequence in between, yes.

Q Right. So amplicons have an identical sequence to that

portion of the sequence of the genome that is being amplified; correct?

A To that portion, yes.

Q And so that portion will have the same nucleotide sequence as is found in that portion of the genomic DNA; correct?

A Yes.

Q Okay. So the primer will have the same sequence and the amplicon will have the same sequence as a portion of the genomic DNA; correct?

A Yes.

Q And that's important because the whole purpose of sequencing is to accurately read the naturally occurring sequence of the woman; correct?

A Correct.

Q Okay. So we have to make exact copies; correct?

A Yes.

Q All right. Now, also you're familiar with the concept of chemical synthesis of DNA; correct?

A Yes.

Q To your knowledge, how long has DNA been chemically synthesized?

A In term of oligonucleotides?

Q Yeah.

A I don't know the exact date, but I know that in the 80's

that was being done.
Q I'm sorry. During the foundation part, and maybe in your declaration, when did you receive your Ph.D.?
A In 1991.
Q And your undergraduate?
A In 1985.
Q Okay. And were you aware at that time that DNA was being chemically synthesized?
A While I was in graduate school, yes.
Q And you're aware that genes had been chemically synthesized; correct?
A Entire genes, the viral genes, yes.
THE COURT: Will you say that one more time.
THE WITNESS: Yes. Some viral genes, yes.
Q (BY MR. GAEDE) Okay. Are you familiar with somatostatin?
A Somatostatin?
Q Yeah.
A No.
Q It's a short peptide. Have you ever heard of that?
A Peptides, yes.
Q Okay. So the somatostatin gene that was chemically synthesized, the human somatostatin gene that was chemically synthesized in 1977, are you aware of that fact?
A No.
Q Okay. You're not aware that Genentech was founded upon

that fact?
A No.
Q You do know who Genentech is?
A Yes.
Q Could you explain for the Court briefly, in case the Court doesn't know, who -- what Genentech is.
A Genentech is a biotechnology company that, among other things, that had antibody technology for recombinant (inaudible).
(THE REPORTER ASKED THE WITNESS TO REPEAT)
A Recombinant antibody technology.
Q Also a protein, such as human growth hormone; correct?
A Yes.
Q Insulin?
A Uh-huh.
Q Right?
A Insulin is a growth hormone, yes.
Q Yeah. And Genentech is widely considered to be one of the pioneers in the biotech industry; correct?
A Yes.
Q And so what Genentech did in 1977 was chemically synthesize a human gene and put it in bacteria and make human somatostatin; isn't that right?
A That's what you say, yes.
Q And you have no reason to believe that the protein wasn't

made, the human protein wasn't made in the bacteria using that chemically synthesized gene; right?

A I know that bacteria can be used to synthesize exogenous genes, yes.

Q Right. So exogenous, you mean not natural genes of bacteria; right?

A Yes.

Q SO you take a human gene, coding for a human gene, you put that in the bacteria and it will make a human protein; correct?

A Correct.

Q And you can do that making a chemically synthesized gene; correct?

A You can if all the elements of the gene are there, yes.

Q Right. The natural coding region and the natural coding of the gene is present; correct?

A And the regulatory elements.

Q Right. You're correct on that as well. Now, the Human Genome Project, you're familiar with that?

A Yes.

Q When was the complete sequence of the human genome first published, entire sequence, to your knowledge?

A Approximately around 2000, but there's always been some debate as to what constitutes the complete genome exactly.

Q Can we agree that at the time of 1994 when Myriad filed

its patent application the complete sequence of the human genome had not been published?

A Yes.

Q Next-gen sequencing, to your knowledge when was that developed?

A There are different methods for doing next-gen sequencing. I would say probably the last -- in the last decade.

Q Okay. And you would agree that next-gen sequencing did not exist as of 1994 when Myriad filed the 282 patent application; correct?

A Not at the time.

Q Yeah. Just a few final points here. Let's go to paragraph 18 of your declaration. Here you talk about what primers do. And primers prime the reaction for the synthesis of DNA that draws upon DNA polymerase; correct?

A Correct.

Q And DNA polymerase is a naturally occurring molecule; correct?

A Correct.

Q And so a primer is being used when being used in a BRCA1 section to make an exact copy of the BRCA1 gene, that portion of the gene; correct?

A In PCR, yes.

Q In PCR, yes. And so it's not being used in that

application to treat some other disease; correct?
A I'm sorry, I don't understand the question exactly. The use --
Q Sorry. You go ahead and finish. Are you finished with your answer?
A I -- could you restate the question?
Q Sure. Let me withdraw the question and state it again. Is the primer being used as a human therapeutic?
A No.
Q Right. It's being used to make a copy of a portion of the naturally occurring genomic sequence; correct?
A In the process of PCR, yes.
Q Yes. And that's so the naturally occurring sequence can be read; correct?
A So that the natural occurring sequence then can be deduced, yes.
THE COURT: Dr. Roa, why do you keep saying in the process of PCR? Is there another application for primers that's relevant to our discussion today?
THE WITNESS: There are other uses for primers, such as primer extension for instance where you make some copies but not in the kind of numbers that PCR would generate. So for PCR you always have a pair and you amplify a sequence that's in between the primers, whereas, primers for instance can be extended and used to make probes, as an example.

Q (BY MR. GAEDE) Just a couple of other questions. You heard Mr. Mangum discuss under section 101 certain issues this morning because you were here in the courtroom; correct?
A Yes.
Q To your knowledge, in 1994 when Myriad filed this patent application, did it develop a new method of using PCR to amplify a portion of the BRCA1 gene?
A No. And in terms of the technology, the technology was there, but the application to BRCA1 was novel.
Q Okay. So Myriad didn't have to make any new inventions in terms of how to amplify a portion of the BRCA1 gene once it had the sequence; correct?
A Correct.
Q Okay. And that's also true for sequencing those portions of the gene; correct?
A There were methods in existence at the time, yes, to do sequencing.
Q Right. And to your knowledge, Myriad did not invent a new method of sequencing at the time the patent was filed with respect to the BRCA1 gene; correct?
A Not in the method, no.
Q Okay. And that's also true with respect to the BRCA2 gene that was filed in late 1995; correct?
A Yeah. Again, it's the application.
Q Okay. By the way, Doctor, do you know Dr. Anne

Bowcock?

A I'm sorry?

Q Do you know of Dr. Anne Bowcock?

A She is or was at the University of Texas Southwestern and was one of the investigators looking for the BRCA1 gene.

Q Right. And Dr. Simon Gregory, do you know of him?

A No, not Dr. Gregory.

Q So you're aware that Dr. Bowcock was working in the field of BRCA1 in 1993, 1994 time frame?

A Yes.

MR. GAEDE: Okay. Thank you, Your Honor. No further questions.

THE COURT: Mr. Jackson, any follow-up?

MR. JACKSON: I have nothing, Your Honor. Thank you.

THE COURT: Dr. Roa, thank you. You may stand down if you'd like.

MR. GAEDE: Your Honor, if you give me one second to change over here. Your Honor, I realized I neglected last time to give you a copy of the slides. I'm sure you have more materials, but in the spirit of you saying you're not opposed to more paper, I've got our presentations and we'll give you a binder here. You can put them in as we go through them in case you want to write any notes on those if that's helpful.

The Court: That would be helpful, thank you.

MR. GAEDE: So here is the first one. I apologize, I forgot to give that to you. But secondly would be the patentability one right here.

Would you all like a copy too?

THE COURT: If you have a second copy.

MR. GAEDE: I'm sure we do. If you could make one. I'll give it to you here in a second. So let me not delay things any longer because I want to make sure we get going.

THE COURT: Does Mr. Mangum have a copy of these slides as well, Mr. Gaede?

MR. GAEDE: No. He hasn't given me his. I'm happy to give it to him.

Would you like a copy?

MR. MANGUM: Sure.

MR. GAEDE: How can you turn it down, more paper.

THE COURT: We do want to ensure, both for the court reporter and for the aid of the Court, that we have complete copies of these. In fact I'll ask both sides to submit after the hearing electronically at our chambers copies of your slide presentations and then we'll -- in fact I'd like you to submit two so we can give one to our court reporter as well. And then I want to ensure that you both exchange those copies so everybody has everything that I've seen and will be relying on; right?

MR. MANGUM: Will do, Your Honor.

MR. GAEDE: No problem. We'll do that, Your Honor.

THE COURT: Great.

MR. GAEDE: Okay. Let's start from what I think is an important principle. Basically going to look at three basic areas, Your Honor, particularly in light of the evidence we just heard and some other evidence that we've submitted to you, that the Myriad Supreme Court decision addressing the invalidated patent eligible subject matter that went to synthesized DNA that has the same sequence as the naturally occurring DNA, the genomic DNA. We'll talk about that for a minute.

Secondly, in any event, the evidence before you establishes that the primer claims do not satisfy the Chakrabarty markedly different test. They make reference to the hand to man. Of course, there's language out of Chakrabarty, but they don't run through the whole Chakrabarty analysis. And that has been done earlier, of course, by Judge Sweet, but the evidence here will show you that the primers do not meet the Chakrabarty test because, after all, what are we arguing about? We're arguing about whether a primer is a product of nature and therefore patent ineligible.

Obviously we're not in this courtroom to argue that the full chromosome is a product of nature. The issue comes down to, the rubber hits the road, as to there's no question

there's some differences because we have a molecule that is not the same as the chromosomal DNA. That's true. That's why we have this dispute because obviously you can't patent the whole chromosome in naturally occurring DNA. No question about that.

So then the question is, okay, how far can you go until something is not a product of nature and is patentable subject matter? Now, you heard Mr. Mangum before the break talk about a couple of examples. There's patents issued on them. With all due respect, the PTO issued a patent on subject matter the Supreme Court struck down. So the fact that the Patent Office has granted a patent on something does not somehow make it patentable subject matter. In fact for 20 years the Patent Office got it wrong. They just got it wrong.

And when you read the Myriad decision, the Supreme Court gave it zero deference to Patent Office policy, and said the issue just hasn't been in front of us. The fact that the Patent Office has been wrong for 20 years doesn't change the fact that the Patent Office is wrong.

And you have to analyze a product of nature under the Chakrabarty analysis, informed by Mayo. We'll talk a little bit about that. But I agree that when you read Myriad, that the Court looks to Chakrabarty, looks to Funk Bros. and those two cases informed by Myriad.

So also you're going to see the positions. They're

estopped also on the principles of collateral and judicial estoppel, because the issue in -- hold on. I'll get to that in one second. Let me get to this and I'll go back.

The Myriad Court had an issue before it just like you do. They were reviewing a judgment, and they're reviewing a judgment to this, to an isolated DNA coding for BRCA1 Polypeptide to the isolated DNA of claim one, to an isolated DNA having at least 15 nucleotides of the DNA of claim one. So the claims all have the word isolated in them.

Now, what's the effect of that? That's the subject matter that was before the Supreme Court. And what did the Supreme Court understand that subject matter to be? We'll talk about that in a minute. But before we get there, I want to show you one other I think very important principle.

This comes out of the June -- I forget the exact date -- June 2013 Ultramercial case by the Federal Circuit. And you'll notice what they say here. I didn't hear any discussion of what the standard is and how you're supposed to assess section 101 in light of the evidence that's been presented to you. Is it a question of law like claim construction or is it also a factual issue?

And the Federal Circuit makes it crystal clear right here in Ultramercial what it is. So first it says while ultimately a legal determination is rife with underlying factual issues. That's important to the question of whether they have shown

that there is no substantial question here, and whether we have raised a substantial question. It's ultimately a factual issue in the context of section 101.

And look at what this -- you heard Mr. Mangum's discussion, and you heard about the various types of language in the Mayo decision. And look what the Federal Circuit says. Factual issues -- this comes about the fifth line -- factual issues may underlie determining whether the patent embraces a scientific principle or abstract idea.

Next it goes on. If the question is whether genuine human contribution is required, and that requires more than a trivial appendix to the underlying abstract idea, and were not at the time of filing routine, well understood, or conventional, factual inquiries likely abound. Almost by definition, analyzing whether something was conventional or routine involves analyzing facts.

So I'm going to go to the Myriad, but what you just heard is that from Dr. Roa and what you have also in the uncontradicted and unaddressed declarations of Dr. Tait is that using the amplification is exactly that, analyzing whether something was conventional or routine, involves analyzing facts. The facts before you establish that there was nothing new in the applications in terms of amplifying or sequencing that high level once you had the BRCA1 and BRCA2 sequence. That's the evidence before you.

THE COURT: I don't think Myriad disputes that. Am I wrong about that, Mr. Mangum? I mean --

MR. MANGUM: That's right. That high level abstraction, that's the very point I was making during my presentation. It's the application of it to the specific circumstance.

MR. GAEDE: And this right here is more than trivial to the underlying abstract idea, and the application was not routine and well known. We'll talk about that. So it's not just enough to say that there's a comparison, I append another element of the claim to that and all of a sudden I'm in patentable subject matter. This makes clear it's a factual issue. It's an ultimate legal issue with underlying factual issues, and we'll talk about how what Myriad's claim do is effectively preempt the gene itself.

But let's go first to the primers. So the subject matter is isolated DNA. And I think it's important when you think about the Myriad decision to focus on a couple facts. One is claim two references cDNA. That's how they characterized it, but the term is isolated DNA that is being addressed in claim two. And because of the reference to the gene, of SEQ ID No:1, that specific cDNA coding region sequence, that means that isolated DNA includes synthesized DNA. Addressed right there in claim two, that subject matter as well in claim one. Isolated can't be construed in different ways in two claims.

And I'll show you why it includes obviously synthesized DNA as well.

But also I think what is important to the argument you heard this morning is claim five. An isolated DNA having at least 15 nucleotides of the DNA of claim one. So that claim was before the Supreme Court, and the Supreme Court found that claim not to be patent eligible.

So they characterized the Supreme Court, and they're aware of this issue, that it wasn't the entire gene we're talking about excising somehow from the genome. We're also talking about shorter sequences. We're talking about, as the Supreme Court says, the practical effect of claim five is to assert a patent on any series of 15 nucleotides that exists in the typical BRCA1 gene.

And interestingly enough, as we'll get to this point, the Court's decision with respect to cDNA didn't rest on the fact that it was chemically synthesized, chemically made in a laboratory using laboratory techniques. It rested -- so that in and of itself doesn't take a product of nature out of a product of nature and make it patent eligible. It rested on the sequence, which was a sequence because of the exons that is not found in nature. So the act of just chemical synthesis is insufficient to take a short 15 nucleotide sequence and take it out of the product of nature exception to patent eligibility.

They also understood that there might -- in the cDNA 15 nucleotides of the claim. And so you got to go back to the claims. And again you remember we talked about the structure and the source limitation that comes from the structure? So this claim is to a sequence of primers that come from the naturally occurring sequence by definition in this claim. It's naturally occurring subject matter that is then in a shortened version in a primer, and it contains -- and if you say it might be broader than that, there's no doubt that it contains that subject matter. And if any of the subject matter in the scope of a claim is unpatentable subject matter, the whole claim is patent ineligible. You can't save part of it.

So there's no question, as you heard Dr. Roa testify, that primers that exactly match the sequence of the BRCA1 gene is within the subject matter of this claim. So that means that patent subject matter is part of the scope of this claim, and that's exactly what the Supreme Court was looking at. Same is true 29 isolated, 15, 16 derived.

Your Honor asked the question at the tutorial that I just wanted to make sure that we answered for you. You asked the question is isolated DNA different than purified DNA. And I thought that this quote from the Federal Circuit decision, Judge Lourie's opinion, sort of elucidated the difference in that, as he says here, isolated DNA (unintelligible) --

(THE REPORTER ASKED COUNSEL TO REPEAT)

Isolated DNA results from human intervention to cleave or synthesize a discrete portion of a native chromosomal DNA. It goes on to write: As the above description indicates, isolated DNA is not just purified DNA. Purification makes pure what was the same material but was combined or contaminated with other materials. Isolated is removed. It is also in the change because it's not the entire genomic sequence. So hopefully that helps in terms of elucidating the difference between the two. And what the subject matter was before the Supreme Court, of course, was not purified DNA. It's isolated DNA.

Seems like we're going to argue over some of the same language in the Supreme Court decision. I'm going to move pretty quickly through this since I know Your Honor has read it, but I think it's important to see how they frame the issue that a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated. So a DNA segment. And, of course, isolated means synthesized or excised in some other fashion out of the cell, merely because the act of isolation doesn't take it out of the product of nature exception.

Mr. Mangum also related to this one, but I think this is an important point. They were certainly aware of the synthetic subject matter with chemically synthesizing before

them. And they write it's also possible to create DNA synthetically through processes similarly well known in the field of genetics. Then it goes on to say one such method to describe cDNA.

The other types about the chemical synthesis were clearly articulated to the Court. We provided to you their brief that say that. I have one quote here. I'll quickly go past that. But there's no question that they understood that isolated DNA constituted as well synthesized DNA, consistent with the construction of the term that -- in the patent claims that were before them.

And then also that they also understood that short DNAs were at issue, not the entire gene, but the short DNAs. As you reflected on the Federal Circuit decision, you notice that in the concurrence Judge Mallick (phonetic) distinguished between the shorter and then the longer sequences of DNA as well.

So no question that everyone understood they're short sequences. Any strand of 15 or more nucleotides within the genes. But it goes on to say, but isolation is necessary to conduct genetic testing. They understood that, that you had to have these tools as they call them, the primer, the amplicons, in order to conduct genetic testing. They understood that fact.

Here are the (unintelligible) --

(The reporter asked counsel to repeat)

Sorry, trying to save some time. I'll go a little slower. Here when they talk about Judge Lourie they also talk about the synthesized point. So there's no question the Supreme Court understood that that was subject matter. And, of course, the cDNA is made by man, synthesized.

The other thing is Judge Sweet and how he construed the term in the District Court where that claim term was expressly before him. And as he made clear in his construction, it includes as well DNA synthesized through chemical or heterologous biological means. So isolated DNA includes this. What did he base that on? There's in the patent the discussion -- the definition that isolated includes synthesized DNA.

And Dr. Kay, who you'll hear from later today, submitted a declaration which is attached to my declaration in which he says one of ordinary skill would understand that isolated DNA has been extracted from the cell and excised from the chromosome, or chemically synthesized.

You've seen this slide before. I don't think there's any debate. You just heard Dr. Roa talk about that, if you have a chemically synthesized gene, it can be used to make a protein and a bacteria chemically synthesized can make a human protein. Again, synthesized DNA has the same functionality as, if you will, a piece of DNA purified out. There's no

difference in the structure, also cloned DNA. All that's the same. DNA is DNA.

And then, of course, the sequence follows the same, ordering of the native nucleotides. They also, of course -- you've seen this in our brief, but you have these quotes in our slides and my second declaration as well that they were representing to the Supreme Court that the primers and isolated DNA molecule, that amplicons are copies of the genomic DNA. As you just heard Dr. Roa say that portion that makes an exact copy of a portion of the BRCA1 DNA. I don't think there's a lot of dispute on that issue.

They also, of course, argue the significant utility that you just heard this morning in terms of an argument. They made that argument to the Supreme Court, and the Supreme Court did not accept Myriad's position.

And I think what's important is where they talk about Chakrabarty. I don't think there's any real dispute that Chakrabarty is applicable here, that the markedly different characteristics is how Judge Sweet looked at it, it's how the Supreme Court looked at it through this here. And what they found is that, of course -- and, remember, claim five, 15 nucleotides was before them. To be sure, it's an important use of a gene, but separating that gene is not an act of invention. And that they contrasted that to Chakrabarty. And, of course, groundbreaking, innovative and brilliant

discovery does not by itself satisfy the section 101 inquiry.

The question is the composition, is it a product of nature, not how it is made because synthesized DNA is the same as natural DNA as cDNA in terms of the structure of DNA. The question is the sequence not the process.

And the claim before you in the primer claims and the claim before the Supreme Court were not process claims for how to make a DNA. They were to a composition of matter. And the question is is whether that composition of matter somehow was no longer a product of nature by virtue of the rest of the genomic DNA being taken away from a particular part of that genomic DNA.

Primers rely on DNA's genetic information. And I think this is important. Claims aren't saved by the fact that isolated from the human genome severs chemical bonds. Why is that important? Because when you're synthesizing DNA you've effectively excised and broken the chemical bonds that exist in that longer strand of DNA. It's not the physical act of the process. It's not a process claim. It's the fact that the product of nature has broken those bonds because it exists separately and doesn't then have the bonds to the rest of the DNA.

Now, you've heard this, but I think this is important again just to emphasize. When it looked to the cDNA, the Supreme Court relied on the exons. Didn't rely on how it's

made, which is clearly a man-made process, clearly a process that was done in a laboratory. Relied on the fact that it's an exons only molecule, which meant that that sequence of DNA does not exist in nature because you have the various parts of the --

THE COURT: It does though, doesn't it? Can't we find it in the mRNA?

MR. GAEDE: You can find it in the mRNA, I agree, that you can find that sequence in the mRNA. But the question is, again, it's a composition of matter claim to a DNA. And a DNA is a structure and is a composition of matter, and that DNA composition of matter does not exist because you have the intervening introns.

So it's not a question of whether you're making a copy of mRNA, which is a different nucleic acid and a different naturally occurring nucleic acid.

THE COURT: But the question under Chakrabarty is whether it exists in nature, right, not whether it exists in a specific place. Does the analysis hold up if we find the same sequence in the mRNA that's in the cDNA?

MR. GAEDE: No, because --

THE COURT: How is that different? How is that different than --

MR. GAEDE: It's different for the reason that we talked about earlier in that the natural -- you're making a

DNA that does not contain the same contiguous sequence of DNA as found in a naturally occurring DNA. That's the difference.

THE COURT: That you're making a DNA?

MR. GAEDE: You're making a DNA. And the claim as to the primer claims and the isolated DNA claims in front of the Supreme Court were to a DNA not an RNA. And that's where they split the difference. I think, you know, you could even argue the cDNA, of course, is a naturally occurring product of nature, but that has been litigated. And the distinction rested on not how made but the sequence itself and that DNA sequence is not found naturally in nature. That segment of DNA does not have that sequence as a contiguous sequence.

And that's in that language that they have that the lab technician in question creates something new because it retains the naturally occurring exons, but it is distinct from the DNA from which it was derived because they're speaking in terms of sequence. The key is sequence not how made.

THE COURT: So let me ask you again then why -- why did the Supreme Court -- looking for a governing principle here. The sequence of the nucleotides found in the mRNA, and I understand that's RNA not DNA, that sequence is identical to the nucleotide sequence that you have in the cDNA, is it not?

MR. GAEDE: It is.

THE COURT: So if it's the sequence that we're focusing on, I guess your answer is the same as what you gave

just a moment ago. I'm comparing RNA against DNA, and that's an apples to oranges comparison here?

MR. GAEDE: Correct. That's absolutely correct.

The COURT: Judge Bryson looks at the cDNA in his opinion I think and compares it against both the DNA, the native DNA, and the RNA, the mRNA. Is that just nonsensical?

MR. GAEDE: I think at the end of the day, Your Honor, is we do have a Supreme Court decision, and they drew the line where they drew the line. And the product of nature and the claim were directed to a DNA, and that isolated DNA, that cDNA sequence, was not naturally found because of the introns.

THE COURT: So we draw ourselves back to the language of the claim, which is focused on DNA?

MR. GAEDE: Correct, because it's a product of nature, and the question is has it been markedly changed, markedly different characteristics such that that DNA is no longer a product of nature.

You've seen this. You've obviously read Judge Sweet's opinion as well, and he addresses the issue more -- in greater detail Myriad in addressing many of the arguments. And I think what you heard this morning was an argument of just differences rather than similarities. And as we talked about, the claims require you to take the sequence from nature. They require you to do that.

And so Judge Sweet looked at this issue and he found that the isolated DNA -- and he found that the applications for which the whole genomic DNA is unsuitable, namely the templates, primers, etcetera. But I think what's important here is exactly what you heard Dr. Roa say, that the sequence is exactly complementary. It draws on the natural principle and the natural structure of the existing sequence for its utility. And that's undisputed when you talk about the structure of the primer, that it operates by binding through natural laws of Watson-Crick base pairing mimicking that portion of the DNA and priming a reaction for DNA synthesis.

And as Judge Sweet found, the basis for this utility is the fact that the isolated DNA possesses the identical nucleotide sequence as the target DNA sequence, thus allowing target specific hybridization between the DNA primer and the portion of the target DNA molecule possessing the corresponding sequence.

And I don't think the experts are in dispute here. You just heard Dr. Roa discuss that, Dr. Pribnow as well. So the evidence before you is that it draws on that principle.

And, of course, as also Judge Sweet talked about the amplicons as well, it draws on maintaining that fidelity of sequence, that it doesn't change compared to the natural genomic sequence so that we can read it.

Now I want to go back because I slipped over this slide

too fast because I think it's important, and I want to make sure this point is clear. This is the Supreme Court talking. And you have the isolated DNA claim, and it talks about severing the bonds, but it also -- Myriad's claims are simply not expressed in terms of chemical composition, nor do they rely in any way on the chemical changes that result from the isolation of a particular section of DNA.

You heard right before lunch these other examples which, of course, it was attorney argument. It's not before you in the record. But, in any event, Myriad's claim here to the primers is not described in terms of somehow changing one group on the DNA. And in fact they are described in terms of reference to the naturally occurring sequence. So that's right in the scope there of the Supreme Court's decision on the primer claims that follow again the isolation claims.

So the evidence before you and that raises substantial question is, first, the primer sequences are isolated from the target. That's a naturally occurring sequence, no question about that. Otherwise, the primers will not be able to anneal to the target DNA.

The amplicons are exact portions of a portion of the DNA, and the fact that something is chemically synthesized doesn't change the property of the DNA in and of itself as compared to cDNA or taking a piece naturally out of a larger piece of DNA, because it's not to a process of how to make it, it's to the

thing itself, which is DNA. And that product of nature is not markedly different, particularly here in these claims where it references the natural sequence. Okay.

THE COURT: Not markedly different how?

MR. GAEDE: Well, first --

THE COURT: Different in purpose is it?

MR. GAEDE: Not really.

THE COURT: Well, it's not being used to build amino acids and proteins; right?

MR. GAEDE: No, but you have to remember, Your Honor, DNA also has to naturally replicate itself. That's one of the other natural processes that goes on in the body as we speak. And so DNA is not just -- functions not just to encode for a protein but also to replicate itself as part of maintaining life itself.

And so that process, what we're doing with the primers, is we're mirroring that process to make an exact copy of the DNA. And so, no, I absolutely disagree given examples. For example, they say, well, you have nucleant therapeutic. No. That's a far more different subject matter than what we have here where what you're doing is harnessing the natural process of DNA replicating itself.

Slight difference with the RNA primers and the DNA primers. You can read that in Dr. Pribnow's second declaration. But the process of DNA replication is what's

being harnessed here.

Okay. I don't think -- I don't think it's a dispute that isolated DNA means synthesized DNA, and they represented that multiple times in the Supreme Court. They argued for that construction at Dr. Kay's declaration before the Court and that was the issue on review. They're estopped.

Here is the collateral estoppel. There's no question there's overlapping subject matter. They're estopped. Issue previously decided is identical to the one presented in this action. Can a short sequence of DNA that's a product of nature, can it be patentable? Supreme Court said no, claim five. That subject matter is not patentable. Fully adjudicated on the merits. It has been. They were present in the prior action, obviously, and had a full and fair opportunity to litigate the issue.

You also have judicial estoppel. Tenth circuit follows the Supreme Court's New Hampshire v. Maine. They're estopped as well from contending that isolated DNA didn't include synthesized DNA subject matter, and the issue of short DNA nucleotides and sequences was not before the Supreme Court. Same factors.

Let's go to the method claims. I think we all agree that Mayo v. Prometheus creates a framework for analysis. Certainly AMP v. Myriad invalidates a simple gene comparison claim. The Federal Circuit twice did that.

I think as you just heard, the asserted claims append routine and noninventive steps, as demonstrated not only by Dr. Roa's testimony but of course the evidence before you. Their own patent specification provides no new inventive steps.

Judge Sweet also found Myriad's subject matter is unpatentable. And we have raised undisputed evidence that the asserted method claims effectively preempt the use of the gene itself. And you can see the undisputed first and second Tait declarations for that evidence that's before you ties back to the Ultramercial, that there's underlying factual issues here.

What's really going on here in Myriad's method claims? What's going on here is the draftsman's art. We know that the gene itself is not patentable subject matter. We know that a woman in order to access her gene has to be able to amplify it and has to be able to read it in some way. We know these facts. And I'll show you here a statement from Myriad's former president under oath in the former litigation which says exactly that.

So what you see in these claims when you start to strip them apart is the draftsman's art to build a fence to that gene itself and to thereby lay claim to the unpatentable subject matter in and of itself, which is the product of nature or the comparison that is going on that is necessary for a woman to understand whether she has a higher risk of

BRCA1 cancer or not, which exists naturally with inside her. There's no dispute about that.

It existed before Myriad got here and it will exist after Myriad is long gone. And that's her information that is inherited from her parents and from her grandparents and from all of her forefathers. And they're saying through their claims you cannot access that without paying us tribute, or in their case no one else can do it.

So I'll get to the claim in a minute, but when you start to strip them apart, where there's a lot of words in there, that's what they're doing. So obviously a law of nature is not patentable and neither is the process reciting a law of nature, unless the process has additional features that provide practical assurance, practical assurance, that the process is more than a drafting effort designed to monopolize the law of nature itself. And I know the Mayo v. Prometheus decision.

And so in all the claims, what we have is a comparison in these method claims or you compare two sequences. And the sequences, of course, are naturally existing. Myriad didn't invent those sequences. The information in those sequences, as you heard, there's information in the sequences existed.

And so the question is what Judge Breyer in the unanimous opinion describes as inventive concept. And it says our cases insist that a process that focuses upon the use of a natural

law also contain other elements or a combination of elements, sometimes referred to as inventive concept, sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself. And as you heard, there's no inventive concept in these other steps. And it also can't be -- the notion cannot be circumvented also by limited to a specific area.

So in the Mayo case, you're right, it's a little bit different claim than what it is before you here. One point I would say, obviously synthetic subject matter was being used in the Mayo claim because it's thiopurine, which is a man-made drug. So the fact that a man-made drug, there is some synthetic subject matter arguably in the claim. That doesn't mean that you're outside the scope of Mayo. That's the Supreme Court.

So I understand what Judge Lourie said with respect to that claim 20, which we have explained to you in Dr. Pribnow's first declaration why it's completely different than the comparison claims that are before you of the gene sequences, but that's the Supreme Court. The simple fact that there might be some synthetic subject matter somewhere in the claim doesn't take it outside the Mayo analysis.

All right. You've heard Mr. Mangum talk about Diehr, Flook. I thought it was interesting when you go look at the Mayo case. They also provided an English case. And they talk

about the natural principle and the mental comparison. And they talk about this also, several unconventional steps, not just the law of nature but also several unconventional steps. And what you just heard and what is uncontradicted before you is that the steps here are not unconventional. They're well known and they just simply took the sequence and then amplified it. Nothing new, nothing unconventional in those other steps.

The Diehr case again -- again is applying to a specific process. But when you're just curing rubber, there's a particular way to do it. Again, unconventional steps. Contrast that with Flook, which we talk about in our papers, and I'll move on from this point. But you don't have the unconventional steps in Myriad's claims.

Also, in this particular context there was some reference in their brief -- we're not saying we preempt the use for all genes. That's irrelevant. The issue is the BRCA1 and/or the BRCA2 gene, and they are preempting there.

And, of course, future innovation. As you've heard Dr. Roa also state, the human genome had not been sequenced. Next-gen sequencing was not in existence at the time. Myriad couldn't have thought of it, but they claim it -- or tried to I should say.

Under the current state of the art -- and this is from Mr. -- President Critchfield in Myriad, and I think this is a

very important admission that's before you, Your Honor. He says in earlier litigation in describing the state of the art, under the current state of the art, the only practical way to obtain a sufficient amount of BRCA1 or BRCA2 genomic DNA for mutation detection purpose is to PCR amplify the genomic DNA in segments.

Okay. That obviously means, as you now know from the technology, primers as well are a necessary part of that PCR and that amplification process. And under the current state the only practical way is to use these tools in steps that they append merely to their claims.

There's also -- you've heard the argument, well, the BRCA1 sequence wasn't known, and therefore we're coming up with a new application because we're applying the BRCA1 sequence. Judge Breyer dealt with that issue in Mayo as well where he expressly referenced the difference between 102 and 103 and 101, and he got it. Because if you make that argument, as he says, this approach of relying on section 102, however, would make the law of nature exception to section 101 patentability a dead letter.

Why is that? Because anytime you discover a new law of nature or discover a new mental abstract process and you're saying that if I append a step to it I'm not subject to 103, 102 because that law of nature or that mental step or that product of nature was unknown. And, therefore, you have no

meaningful life in section 101 if you say that the sequence has to be known. And he addressed that right in the Mayo opinion. And you have the cites here for you. And their argument is directly contrary to Mayo.

So briefly we've been over the claims. Obviously claim one of the 441 patent is invalid by both Judge Sweet and the Federal Circuit. The question is whether you append a claim of comparing, which of course is the heart of the claim, by amplifying, using a set of primers to produce amplified nucleic acids and sequencing the amplified nucleic acids that effectively preempts the use of the gene itself for comparison. Well, it does. You heard Mr. Critchfield say that in his declaration. You have Dr. Tait's declaration which establishes that fact before you.

There's a whole list. You have the slides. But in brief, probes and amplification prior to sequencing were routine -- uncontradicted. The undisputed steps where they contain no new inventive concept. They effectively preempt a woman's ability to compare her gene sequence through gathering steps, data gathering steps of probing or amplifying. The patent specification identifies no new techniques for probing or amplification. Declarations are uncontradicted to this effect. We have raised undisputed evidence that there's a substantial question.

And, you know, Judge Sweet did go on and address this

issue in his opinion. And he says, in looking at the comparison claims that were -- that his decision was confirmed by the Federal Circuit, he says that even if the method claims-in-suit were construed to include the physical transformations associated with isolating and sequencing DNA, it would still fail because the mere data gathering steps and they effectively preempt the right to use your genetic information in a comparison.

Claim two, same thing of the 857. It's invalid by the Federal Circuit. It's a gene comparison. That's the heart of the claim. This is what I talk about the draftsman's art. If you go down this list here, this is a Markush claim where they're thinking of every way that you could get access to that gene potentially, and then laying it all out in the alternative. They're taking possession of the gene.

You can't get the gene unless you can amplify it. You can't get the gene unless you can sequence it. And you can't perform the comparison that is all right and is a natural law and a mental abstract process that all of us have the right to perform, and even more so screening for a point mutation in said tissue sample. Some of the claims that were invalidated before the Federal Circuit and by Judge Sweet include the language screening, invalid subject matter.

In the reply they try to hang on the word assay, which is up here is determined by an assay selected from the group

consisting of. They say that's a physical test, Well, yeah, you have to perform a physical test in order to screen. There's no question about that. And so they by this claim lay claim to the gene itself. You can't perform the mental comparison which is unpatentable subject matter.

Very similar on the points here. I won't go through it. I'm going to go on to the next claim. Again, this is just a method for determining. So you're determining the nucleotide sequence of the BRCA1 gene. That's just a mental step. You're comparing to another sequence, and then you're determining the presence of the following nucleotide variations. That, of course, exists in all of us, so you're just determining and you're comparing. And then for the specific naturally occurring variations that exist, they're not something Myriad invented. They're Something that just exists.

And what does claim five that they're asserting against us append? Just simply where the gene is amplified prior to nucleotide sequencing. Take Dr. Critchfield's declaration. You have to amplify, and you have to sequence. That's the uncontradicted evidence before you. Here is a summary that you will have.

Same thing in terms of claim two. You have to amplify. You have to sequence in order to determine, because we have to have sufficient subject matter. And there's no new novel or

inventive step or inventive concept in these other steps. They do try to point to these down here, the specific Polymorphisms in the variations, but those of course are naturally occurring. There's nothing new and there's nothing patentable in that. That's not something that Myriad can invent. It naturally occurs.

And, again, to determine whether you have correlation (unintelligible)--

(THE REPORTER ASKED COUNSEL TO REPEAT)

It's a method claim and a correlation for an absence of increased genetic susceptibility to breast or ovarian cancer. Same with claim four, the 155 patent. Same point, we'll have that for you. Thank you.

THE COURT: Thank you.

Mr. Mangum.

MR. MANGUM: Would you like to continue on 101 or are we ready to move on to the next module or what's your --

THE COURT: Well, I know you have more to say about 101. We'll hear that next time. I think I understand where we are.

MR. MANGUM: Okay, fine.

THE COURT: Let's move on to our next module, which is what?

MR. MANGUM: This is the 102, 103, 112, and Mr. Singer will address those issues.

THE COURT: I'll tell you what. Why don't we do this. We've been going for about an hour and a half since we came in, just short of that, but let's take a short break and then come back and just plan to push through to 5:00 o'clock or so. So we'll break for 10 or 12 minutes and then come back.

(RECESS FROM 3:11 pm UNTIL 3:36 pm)

THE COURT: All right. We're back on the record.

MR. SINGER: May it please the Court, Jonathan Singer. We haven't had a chance to meet, Your Honor. On behalf of Myriad, I'll be talking about the issues of -- validity issues separate for the issues raised by Defendants.

THE COURT: Thank you, Mr. Singer. The floor is yours.

MR. SINGER: Just by way of introduction, Your Honor, defense have raised an awful lot of material, a lot of which is highly technical.

The COURT: I had not noticed that.

MR. SINGER: And I'm mindful of your comment that you said you want to try to look at the forest today and not the trees, and we'll have closing argument. So what I'm going to try to do is I'm going to limit myself, not knowing what Mr. Gaede is going to emphasize, what his team is going to emphasize, to the arguments in the brief. If things are

argued about the declaration, I'll address those in the final arguments, and also try to keep it at a higher level to explain concepts in the law that I think are important here for you to keep in mind.

THE COURT: I appreciate that. I also realize that it's just a little bit unfair to the Plaintiffs that we're not allowing you a reply today. It's your motion. You're going to have the last word at the end of the day. It's your burden. You have to carry it. I just think we need to get through it, and I generally understand.

The briefing was very helpful from both sides. There was a lot of it, but you pretty clearly set forth your opinions. I think I know where we are generally, but, please, go ahead.

MR. SINGER: That's certainly better than the alternative. I've put this together, Your Honor. These are the arguments from the Defendants' brief. I've not put anything in here that was only addressed in the declaration.

And there's just a piece of common sense I think we need to keep in mind. There's a lot of issues here, but none of it at the end of the day should detract from sort of a common sense notion here, that if these patents do in fact cover patentable subject matter under 101, and I think Mr. Mangum has demonstrated so amply today and will, I'm sure, at the closing, that these patents cover a genuine discovery worthy

of protection under the other provisions of the patent act.

There's a reason, right, it was the lead story on NBC News. This was a revolutionary discovery for its time, very difficult process to do it, and a very unusual result at the end of the day. And it's not anticipated by the prior art, and it's not obvious in the prior art. And one or two claims that they say are not described are in fact described.

So let me start with the issue of anticipation. The Defendants, of course, bear the burden of proof at the end of the day on invalidity, and it's important to keep in mind that that standard is higher; right? And it also applies to the 101 argument. It's clear and convincing evidence, not simply a preponderance. And they must raise a substantial question of validity on all the asserted claims.

Anticipation, one reference; obviousness -- obviousness, of course, more than one reference. Anticipation, one reference, identity, expressly or inherently in that one reference, all elements of the claims. If one element is missing, end of anticipation.

Okay. Let's talk and start sort of the same organizational principle that we already had. I'm going to start with the primer pair patents. I've actually lumped them together a little bit differently, Your Honor, based on sort of the invention, if you will, than we heard before because I think it's easier from this perspective looking at them this

way.

We've got the primer pair patents and the method patents, which are an obvious issue only in the briefs. And I'm just putting the BRCA claims together, the BRCA1, BRCA2, and then what we're calling the consensus sequence claims. And I think that's an easier way to look at the obviousness issue. And hopefully, you know, if there are issues raised by Defendants, that that organization will hold for you.

Okay. Let's go to the primer pair patents. And as I say here, I start off you've got three main points that I want to talk about. And the first is a claim construction issue, which is actually fairly important. And as was pointed out repeatedly, of course, this is something for the court to determine independent of any fact issues.

And when you actually look at Defendants' anticipation arguments, Your Honor, they hinge upon an erroneous claim construction, that essentially in the primer pair patents assigns the same scope of the independent claim to the dependent claim.

If you look at what their experts say, and I'll show you in a minute, the experts look at the independent claim and the dependent claim and assign them fundamentally the same scope, which is why they rely on the same prior art to anticipate those claims in both the BRCA patents, BRCA1 patent and the BRCA2 patent.

How do they do that? So here are the primer pair patents. And we see we have an independent claim and a dependent claim. I think as we all know now, SEQ ID NO:1 in the BRCA1 patent, that is the exons only sequence, i.e., the cDNA.

Just on its face, right, claim 16 should have, as is presumed, a different scope than claim 17. Same is true BRCA2. SEQ ID 1 in that patent is the cDNA of BRCA2. Claim 30 talks about the BRCA2 gene having the nucleotide sequence set forth in SEQ ID 1, i.e., the cDNA. Claim 29, the independent claim does not have that requirement. Same across the board on both patents.

What do the experts or Defendants do in applying the prior art to those claims? I think they make some arguments that they're indefinite. And I'm not going to get into that because I think the Court will see in the case law that unless there's just no construction the Court can reach on the claims, and I'll be happy to address it in closing, unless there's no construction that you can reach, the claims are not indefinite.

The Court: I don't think we need to spend a lot of time on that.

MR. SINGER: Right, Okay. And so what is Dr. Gregory saying here. He's saying I couldn't understand the claims. They were indefinite. But when I look at the

dependent claim, what that means to me is that the corresponding cDNA of the BRCA1 gene is in SEQ ID NO:1, not that the primer pairs have to amplify the cDNA or a portion of the cDNA, but the corresponding cDNA of the amplicon is in SEQ ID NO:1.

And, of course, the corresponding cDNA of an amplicon -- excuse me. The corresponding -- the corresponding cDNA of an amplicon that has SEQ ID 1 is going to be the genomic DNA, which of course is in the independent claim.

So they say, nonetheless, for the purpose of comparing claim 17, I assume that claim 17 means that the primer pairs amplify a fragment of the BRCA1 genomic sequence, right? So anything. And that the corresponding DNA is SEQ ID No:1, not that it has to amplify the cDNA. Same for 29 and 30.

So they're assigning the identical scope through -- through a claim that they don't understand the claims and then say, well, to make sense of them, this is what I'm going to do. That's not what the claims say. I think this is a fairly straightforward claim construction issue for the court governed by Federal Circuit precedent, and it can be resolved readily. And it puts an end to all of the anticipation arguments.

If you look at the claims of the primer pair patent, you will see -- not quite all, most all. I should be a little more careful with my words. Look at the claims 16 and 17.

You can see -- and Mr. Gaede I think when he was talking about infringement reminded the Court, and he was correct, that the first source of claim construction is the plain language of the claim. And we have two different claims with two different claim languages.

17 says the BRCA1 has the nucleotide sequence set forth in SEQ ID NO:1. Claim 16 just uses the term BRCA1, ergo, the proper construction from the claims should be that the BRCA1 gene must at a minimum encompass SEQ ID NO:1. It also encompasses the genomic DNA, but it also must, based on the claim structure, encompass SEQ ID NO:1. And that is the proper construction. 17 is SEQ ID NO:1. 16 encompasses it. It's the independent claim. 17 then, as the patent law requires, further narrows claim 16 with its additional limitation that the BRCA gene has to have that sequence.

We cited the Allergan case, Your Honor. And I actually -- this is a case I argued with the Federal Circuit. It's right on point. In that case the independent claim -- this is a chemical case. And in chemistry you see all the structures that are out there, and oftentimes, rather than specify a particular -- you saw the hydroxyl group. Rather than specify that, chemists will just put an R there, and that means you can have multiple substitutions where that might be. And the way this claim was was N(R)4 2. And what that meant was you have a nitrogen, and then an R 4, which meant, okay, R

4 could be the claim then specified a bunch of different things it could be. And they had a 2 there. The dependent claim in the case had N(R) 4 2 where the R 4's weren't identical. And you might look at that and say, well, N(R) 4 2 that means the -- there must be two of those R 4's, and maybe that means they're identical, maybe it doesn't mean they're identical. How am I supposed to figure that out.

Well, they looked at the dependent claims, right, and the dependent claims, they weren't identical. And the Federal Circuit said, okay, we have a construction on the one hand from the Plaintiff in that case that says the dependent claim is given meaning if you say R 4 are not identical. And, on the other hand, we have a construction from the Defendants in this case that says, oh, no, no, that dependent claim is nonsensical, in this case not infringed, because the R 4's have to be identical, and it doesn't cover what is explicitly recited in the claim.

The Federal Circuit said, no, no, no. That's not what we do. We look at the claims. We construe them to make sense. And in this case the way they made sense was to construe the R 4's not identical. Just here the same thing. We construe the term BRCA1 gene and BRCA2 gene to include the cDNA sequence that is then identified in the dependent claim.

And this isn't a case, Your Honor, where the specification is somehow inconsistent. The specification is

exactly consistent and says the same thing. This is the definition section that both parties have gone to to look at how do you define BRCA1 gene. And there's a definition section. The patent, of course, we have -- we have to apply those within their bounds. And I put a little kind of asterisk there at the top because it talks about BRCA1 gene and talks about it being defined, because Defendants would have you stop reading where I put those asterisks.

They say, well, BRCA1 gene is likely expressed in normal tissue which is in the BRCA1 gene, so -- region, therefore, it must be the genomic DNA. That's how they get their argument. BRCA1 gene, genomic DNA, this makes no sense to have BRCA1 then meet the cDNA. But if you continue to read, you see it explicitly references SEQ ID No:1 right there. These terms, when applied to nucleic acid, refer to nucleic acid which encodes a BRCA1 polypeptide. And then it gives the coding sequence for a BRCA1 polypeptide as shown in SEQ ID NO:1, i.e., the BRCA gene must be able to encode for SEQ ID NO:1 -- or excuse me -- the polypeptide that's shown in SEQ ID NO:1. BRCA1 gene encompasses the cDNA.

And if it need be any clearer, it goes on to say that the Polynucleotide compositions of this invention include, and then it lists cDNA. So the specification is at one with the structure of the claims, and the construction the Defendants have offered you in support of their anticipation arguments,

most of them, is erroneous and should not be adopted by this court.

And I've put here, Your Honor, why this is the proper claim construction, claim 16, 29 of -- put them together for you since they're quite similar for the BRCA1, BRCA2. A pair of single-stranded DNA primers, and there are, of course, other limitations in the claim, amplifies a sequence that is all or part of the BRCA1/2 gene.

Claim 17/30, pair of single-stranded DNA primers, amplifies sequence that is all or part of SEQ ID NO:1, i.e., BRCA1/2 cDNA. The BRCA1/2 gene encompasses the genomic DNA, it encompasses cDNA and the other things listed in the definition.

All right. So that is really the scope of the claims that applies to most of the arguments being made. I'm going to go a little bit into the trees here and talk about the prior art itself, with the expectation that we'll have a chance at closing, Your Honor, to do it in a little more rigorous fashion, little more detail.

Really four -- really three pieces of prior art raised against the 282 patent, and just one against the 492 patent. I'll discuss the 282 patent first.

Okay. And this is very straight forward. Now that we see the proper claim construction, the prior art starts to fall away. And that's what's going on here. They're putting

forward a claim construction not supported by the plain language of the claims, not consistent with that construction in the specification to then bring this prior art in. Let me talk about the dependent claims first, then the independent claims.

So we have dependent claim 17. Again, that's the BRCA1 cDNA. As conceded, or I don't think there's any argument here, that the primer pair in Abel and Anderson is intron only. So you are not going to meet the limitation of claim 17 of SEQ ID NO:1, so it can't anticipate.

The marker deposits also. I don't think there's any dispute that the marker deposits, which, you know, we don't think can be used as primers at all, but put that aside, that they're also in the intron region. Again, that dependent claim primer to cDNA can't be anticipated by intron-only, if you will, prior art. That's it. Just that simple.

As to the independent claim, Your Honor, this is a tricky issue. The claims has a preamble. And, you know, the Court, as we've talked about, doesn't need to find in our favor on more than one claim. And we don't have to address this issue if you don't want because claim 17 is clearly not anticipated. It's patentable subject matter, and it's not going to be obvious either, which I'll show you in a minute.

But claim 16, if the Court wants to address it, the Defendants dispense with a large portion of the claim. The

claim has a preamble right there, for determination of a nucleotide sequence of a BRCA1 gene by a polymerase chain reaction. The primer pairs have to be for that purpose.

And the case law is quite clear that language in a claim preamble has limitation or limits a claim if it recites essential structure or steps, or necessary to give life, meaning and vitality, or, also, if it gives antecedent basis.

So preambles can be, Your Honor, in the patent law, they can be just as Defendants claim, intended uses, that is possible. It's not that they're arguing something that's impossible under the law that these things would just be intended uses, it's just incorrect in this instance. And you can see it just by looking at the claim.

Put aside -- just look at the antecedent basis. You need -- the antecedent basis alone tells you that the preamble is a limitation. But, also, this is, if you will, the essence of the invention. These primers are for determining a nucleotide sequence of the BRCA1 gene, in the case of claim 16 and in the case of claim 17 that BRCA1 gene being cDNA. That's the purpose of the primers. It gives life and meaning to the claim. That was the invention. So there are limitations in the claim and they need to be met by the prior art.

Defendants essentially -- and we cited the Vizio case, and I think there's been some argument about, well, it's a

composition claim so it has to be an intended use. The Vizio case is talking about a composition claim, or in that case it was an electronic invention. I'm not sure composition is the -- apparatus, that's probably the better word. It's an apparatus claim for decoding. And the Federal Circuit said, no, that's not just an intended use. That is the, if you will, giving life and meaning to the invention at issue here. It's the same thing. The primers don't exist independent of being able to encode for the BRCA1 gene in the independent claim and in the cDNA dependent claim.

And if you look at the analysis you've been given, Your Honor, it just ignores it. And it's not our burden to demonstrate that the patents are valid. They must come to you with a substantial issue, and they can't get there by just simply ignoring these limitations. There's Dr. Bowcock's declaration, for example, in a claim chart in appendix one. This is her analysis of the marker prior art, and just dispenses with it. The intended use, not a claim limitation. Intended use, not a claim limitation.

And the reason they're doing that in the case of markers is because these things weren't used for PCR. They're not used for determining a nucleotide sequence of a BRCA1 gene. So it's just inconvenient that those limitations are required. They're not met by the prior art in any way, as demonstrated in our brief. And you can't simply dispense with them to

create a substantial issue at this stage of the proceedings.

Okay. That's really it on the 282 patent. The erroneous claim construction dispenses with the dependent claim, prior art, intron only. And then on the independent claims, because those, of course, do cover amplifying introns, the preamble, as I've described, is not met.

Okay. Turning now to the 492 patent, the Schutte art. Mr. Swedlund is dutifully waiting out in the hallway. He's not in here. He's waiting in the hallway. He'll come and testify very briefly, Your Honor, just to lay a few additional lines of foundation this morning just for the Court's benefit.

But the Schutte art was not prior art. The inventors of the Myriad patents had come up with primers that meet, if you will, the essence of what are the exactitude actually of what Schutte discloses. And this is a basic proposition. I'm not going to go into great detail, but people can swear behind, right, prior art. That is not a statutory bar. There's the one year stuff. You can't get behind that. We have that now. In the future we won't have that anymore, the absolute novelty. But there's the one year. You can't get behind that.

But this prior art is in that intervening one year period, and if that's the case, people can swear behind that and show that, oh, no, no, that's not prior art to me; right? Might be prior art to the rest of the world, but not to me

because we had what was in that reference before that reference was available to the public. Just that simple. That's our old system, invention first. Our new system is not that anymore. That's our old system. These patents, of course, come under the old system.

The dates, as you see, we quibble with the 102(g) date as to whether that's proper. But it doesn't matter, Your Honor, whether you use either of their 102(g) dates, the one that we believe is improper, the article received, or the one that we believe is proper, article accepted -- or actually publication perhaps. It doesn't matter. The primers that Mr. Swedlund identified in his declaration done by Dr. Tavtigian meet those dates. And there's just the point of law that I just said.

And here is Mr. Swedlund's declaration. As I said, it will come in very shortly and give a few extra points about where he found the documents. I think that was the question from their side is where was this document, since he wasn't employed at Myriad at the time.

And as Mr. Swedlund's declaration says, the pair -- it was a pair of single-stranded DNA primers greater than 15 nucleotides in length. And if you take their kind of point of view, Your Honor, that you don't need to consider the preambles, it was used in the same way that was used in Schutte. And that's what we said in our brief.

If you sort of adopt their view of the world and how

these claims work, that the preambles don't, and you don't have to know that you're sequencing the BRCA1 -- excuse me -- in this case the BRCA2 gene, and that you're not using it to sequence exons because you don't know that, certainly these primers meet that limitation clearly. They both ended up actually amplifying things that were exonic, so they actually meet also any contention on a dependent claim. And it wasn't, of course, known at the time they did them that that's what they did, so they disclose every bit of what Schutte's prior art reference does, exact same disclosure and prior in time.

There it is. It's -- you've got to have really good eyes, Your Honor, to see it on this. I'm not sure we were smart enough to highlight it on the document we gave you but it's right here highlighted. And, of course, we will get you presentations. I think maybe we'll include a slide that maybe blows that up a little bit so it's a little easier to see. And the date, of course, prints out at the top as to when the printout was made or the program that was used. And as you'll hear, it's the same -- it's the program that's referenced in the patent. It's what people of skill in the art use.

And just very briefly, Your Honor, because it -- I think it's quite clear that for this stage of the proceeding there -- this is prior Schutte reference and not prior art. Even if it is, again you have the same issues as in the other claims. The amplicons in Schutte, one was intron only and one

was intron-exon, or the amplicons that would be produced I think is a better way of putting it. The claim requires exon for claim 30. And again on claim 29 the Defendants' experts do not account for the claim preambles. Can't raise a substantial issue by simply dispensing with them.

All right. Last point on anticipation, then we'll move to obviousness, and this will be very short. It's fair to say that it's a highly technical argument that markers deposited or double-stranded DNA molecules somehow anticipate these claims to single-stranded primers. And I think the scientists debate as to what that really means and would someone really ever do this? I think that's the debate that was going on between Dr. Kay and their experts. Would someone ever do this; right?

And I think they're trying to be fair when they say, well, it's possible that you could do this. I think Dr. Kay can speak for himself, but our view is no one would ever do this. This Is not what people are doing in PCR. But that's an interesting debate, and I think if the court is required to resolve it for this proceeding, you should come down on our side of that point. And why? Well, first off there's no evidence that this was ever actually done. Prior art requires identity; right? You have to have two single-stranded primers used for PCR to amplify -- capable of amplifying the particular sequences.

Taking a double-stranded deposit and having to do all the things that Defendants' experts say you have to do, implausible as that might be, is not identity. It's something different. It's a different argument. It's not identity of disclosure of the language of the claim.

And just to summarize, Your Honor, this goes right back to the tutorial. I mean the Court was shown how PCR works, and the idea behind the primers is that they shouldn't be -- they should be complementary to each other because then they'll bind to each other as opposed to binding to the sequence that you're trying to amplify.

And that's, of course, the problem with the double-stranded DNA. You heat it up and it denatures but then, of course, it will bind back together. And that's why people would not use it in this fashion and did not use it in this fashion.

Okay. Let's move on to obviousness, which I think will be -- I can be a little -- we can be a little less precise because it's a less precise defense. Anticipation is a very precise defense. We need to look at the exact language of the claim. And defendants have that clear and convincing evidence burden at this stage, the burden to show a substantial issue under that burden with the exact language of the claim. Obviousness, of course, the prior art by its nature doesn't have (inaudible) --

(THE REPORTER ASKED COUNSEL TO REPEAT)

Everything that's in the claim. That's the nature of the obviousness defense. And then I'll talk very briefly at the end, Your Honor, about discretion before we put Mr. Swedlund on the stand.

Okay. Obviousness, this is the Graham case both sides have cited. These are the well known factors that one considers in the obviousness inquiry. I'm going to focus on really one, two and four. The level of ordinary skill in the art doesn't really appear to be much in dispute between the parties and wouldn't be an issue of great moment at this stage of the case in any event.

This is the -- I think it's fair to say that they're talking about obvious to try here in these kind of cases from the Federal Circuit. There are many, many that talk about them. Motivated to combine the teachings of the prior art to achieve, have to have a reasonable expectation of achieving the claimed invention.

And then a critical point for the Court when assessing this issue. You don't use the patent as a road map to find the invention. And it's hard. You know, this is not an easy exercise, obviousness, for a court because we have a success in this courtroom. The inventors of the Myriad patents succeeded in this hunt for this gene, and they succeeded by doing things unconventionally in different and difficult ways

and got a result that itself is surprising.

But now it's 20 years later, and we look at that and we go -- and people can find genes left and right it seems. But that's not what we do, and it's very hard to avoid that temptation. And I'll talk a little bit more about this at the end again.

And as you can see, the inventor's own path never leads to invention. That is hindsight. That probably is the BRCA method claims just because what the parties are arguing about is was it obvious to discover BRCA1 and BRCA2? Despite all the plaudits we saw, was that nonetheless obvious?

And I'm going to talk about the state of the art not in terms of the public or press, but let's talk about the state of the art in terms of molecular biology because that's what matters and that's what the Court is supposed to do.

And we've heard a lot about the Human Genome Project being years from conclusion. Well, that's -- you're darn right, it was years from conclusion when these folks made the discovery that they did. And unknown number of genes in the human genome. Full sequence of the genome not even close to being available for purposes of the study. These unidentified genes coined BRCA1 and BRCA2.

And it's important -- I read the tutorial with interest about the difficulties of vocabulary. And it's important to keep -- to understand that just because someone called them

BRCA1 before, that doesn't mean anybody knew where they were, right, or knew how to find them in any particular way. They had a name. Doesn't mean they were obvious.

No protein products identified. So we'll see that's very important in the case law. And extremely large regions thought to contain the genes. They were localized, yes. They weren't looking on any chromosome. We were looking on one chromosome, and, yes, we had it down to a region. But it's important to keep in mind these are enormous regions. I mean this is not, you know, I'm just going down the block. It's one of three houses. I've got to find that one house. We're talking about a huge city that we're looking in as a fairer way to look about this.

Millions of base pairs in the regions that were being looked for BRCA1, BRCA2 no less than 900,000. There's a dispute between the sides as to how large the area is, but, nonetheless, a very large area, given that people thought the average size of a gene, or that there was one gene every 30,000 base pairs at the time. Dr. Bowcock's article talks about that. That's what people thought at the time.

Okay. There's really only one case that the parties have cited that really is kind of in a fully approved version. You know, the Federal Circuit hasn't said, oh, that part of that case is wrong, and that part -- you know how they do that.

In re Kubin, and that is the most recent Federal Circuit

teaching on the obviousness of these types of claims. And when you look at the facts of Kubin, which finds nucleic acid unpatentable, you will see a stark difference than what we see in the state of the art here. And I've listed, if you will, sort of the key points there. That's the case about the nail protein, if the court hasn't read it. And in that case, right, the protein was identified in the prior art. It was an antibody specific to the protein. And that same prior art reference described a process for cloning nucleic acid molecules encoding the protein using the antibody.

So we heard a lot of talk about road maps. That's a road map. And what they were doing in that case, right, is prior to Kubin. Even those facts oftentimes led to conclusions that the nucleic acid was not obvious, Deuel, Bell, those cases. And what the Federal Circuit said, no, we've got a change in the law. KSR has meaning in Molecular biology as well.

So if you have an identified protein, and you've got an antibody specific to the protein, and you have a process described how to clone it, well, that is going to be obvious. And that's what they ruled. None of that available to the Myriad inventors, none.

And the other part of Kubin that I think gets less play -- Your Honor, it caused a stir in the molecular biology community, as you might imagine. It's the case that changed the rules, if you will. But the Federal Circuit went out of

its way. Chief Judge Rader wrote the opinion and went out of his way to emphasize, by the way, I'm not telling you that this is somehow a change, other than what KSR, and emphasized what is not obvious to try in here. And these are quotes from in re O'Farrell, which is sort of the foundational biotechnology case from the Federal Circuit, one of the very early ones. And he's quoting and explaining that if the inventor has a lot of choices, very -- lots of parameters, try a lot of possible choices, that is not obvious. And those that -- that those choices might be things that are out there doesn't make it obvious either.

Second scenario. Not obvious to try a general approach in a promising field of experimentation. Not obvious to do that either. You need to have specific instruction in the prior art in this area to find something obvious.

And you can see just by looking at the science Defendants are using hindsight. They're violating both scenarios that are laid out in Kubin, and violating the basic sort of fundamental one, two, three, four of Graham versus John Deere.

I'll spend about five minutes on this and then we'll conclude obviousness. Just where to look for the gene, dispute between the parties. Where do you look for it? I think it's fair to say from Dr. Kay, who will explain himself, there are a lot of different possibilities in even the locations where it had been confined down to. We put forward

this chart for Your Honor and these are the prior art references, which show these are what the prior art is saying. Look here. It's in this region. These are, by the way, big regions where they're broad, and relatively big regions when they're narrow.

But you can see even as late, right, as November and May of 1994, they don't include where the gene was ultimately found. And this is at the time of the invention, these articles by peers. These are peer reviewed literature of publishing regions which don't include the gene. Where to look for it? Uncertain in the prior art. Lots of approaches. Candidate genes. Talked about those in the tutorial, but that's just taking genes that have been identified and trying out and seeing whether or not they're the right ones associated with breast cancer. They might have been associated with another disease, maybe they'll be associated with breast cancer. You can do that. That's things that people try, and you see it in the prior art, all these other approaches.

And the Myriad folks describe these possible approaches you can take in their patent. And I think it's fair to say Defendant looked at that and said, well, see, those are techniques that Myriad people didn't invent, so therefore this is obvious. Having tools, using regular established tools to find something, doesn't make what you find obvious. That is

Hornbook obviousness law. If that were the case, the number of patents that we would strip from the books would be staggering.

The inventors though, even in applying some of these techniques that were used in the art, they came up with their own way of doing it, right? They had access to unique familial data, right, and they used a hybridization technique that they describe and came up with on their own to do that.

The other two things talked about in the patents, the YACs. I'm not going to get into the technology, but just someone described it to me yesterday, my colleagues who are experts in this area, it's trying to assemble a map of the United States from clones, and in this case the pieces being the various states, but without the outside borders of the United States, and pieces where you might have a piece of the State of Utah erroneously attached to a piece of the State of North Carolina.

That's what it is trying to map with these clones. They're imperfect, they're imprecise, and you don't know how they end up at the end of the day fitting into the puzzle. It's the inventors who came up with how they fit into the puzzle.

Also, lastly, the assembly of the sequences. The gene is of unknown length, size, and the starting and ending points. You don't know where it starts. You don't know where it

stops, you don't know how big it is, and you don't know how big the coding sequences are.

And all of that shows you that this was an art with a lot of choices to be made by the inventors, and they used the exercise of inventive skill to come up with finding the BRCA1 and BRCA2 genes.

Okay. I want to close the obviousness section on these claims, Your Honor, and go to the what I call the consensus sequence claims with the objective indicia. And it's not for any -- I mean these are things that we like to call the common sense factors, okay? You know, I've got this technical analysis. I've put together A, B, C. How do I break the tie? How do I figure out whether this is obvious or not?

And that's why courts say they're so useful. They often are the most probative and cogent evidence of nonobviousness in the record. They check against this tendency to use hindsight. Say, well, they succeeded. They used tools that were available in the art, so could someone else. Because knowing that the inventors succeeded, a fact finder might develop a hunch that the claimed invention was obvious, and then construct a selective version of the facts that confirms the hunch.

This is precisely why the Supreme Court -- talked a lot today about the Supreme Court -- Supreme Court explained that objective considerations might prevent a fact finder from

falling into such a trap.

The objective evidence here is overwhelming. The long-felt need for these tests, undeniable. That goes into the hunt; right? You have a long-felt need for something, the idea being someone should have discovered it sooner than they did in the years of effort that it took to find.

Recognition and praise we saw. Go into it very briefly again. Unexpected results I'll talk about. Commercial success of these tests. Federal Circuit has recognized that commercial success is a very important obviousness factor.

And failure of others to identify the genes at the same time. We saw even coming up with the wrong regions just the month before, or month of the patent being filed.

The praise. We saw all this. I don't need to repeat it again. But these, again, clear evidence that this -- this gene, finding this gene -- and I recognize the come back was, well, the gene itself isn't patentable, but that doesn't mean finding the gene was obvious, which is what the Defendants would have you believe. No. All that praise shows you that this was regarded both in the popular press and everywhere else as a landmark important discovery.

Unexpected results. And this is something that we haven't really talked about except in just sort of glancing, but this gene is really, really big, and that's really, really unusual. When you look -- for example, I think I mentioned

Dr. Bowcock's paper talking about one gene every 30,000 base pairs, this gene, the BRCA1 gene, is 100,000 base pairs. BRCA2 is 70,000 base pairs. A large number of exons, and each gene includes an extremely large exon.

And the reason that's important is these large genes are unstable, makes them harder to find, as Dr. Kay has explained, and harder to work with if you think you've got something. So as a surprising unexpected result that we see a gene this large come out of the hunt that was underway.

And then lastly I think the failure of others. And this is not something we say lightly. I mean Defendants' own experts failed to find the gene. There's been some argument in the briefs that there was simultaneous invention. There wasn't simultaneous invention. It was simultaneous failure is what there was.

Dr. Bowcock's research group did not identify BRCA1, despite having what she says is a road map to do so. Dr. Gregory's research group identified an incomplete and incorrect BRCA2 sequence in December 1995, the same time the BRCA2 patent was filed.

And even going back to show how difficult this was -- and this is -- this is relevant to show both a failure, but really it's more about how hard this really is. Dr. Bowcock, an esteemed scientist, in 1990 published an article excluding chromosome 13 as the size of a primary -- as the site of a

primary lesion for human breast cancer. And, of course, ultimately BRCA2 was discovered on chromosome 13. That's no knock on her. It just shows how difficult and unpredictable the science was at the time the inventions were made, just that simple.

Okay. I will quickly go over the consensus sequence method claims, and I've called them that because what these claims are really getting at, Your Honor -- where is it? Is they cover methods for ruling out common benign alterations in the BRCA1 gene. And they're different than the BRCA claims I called because, you know, the point of novelty or nonobviousness, as the case may be, is not the gene itself because the genes were not known; right? The genes are in fact prior art.

And first off just want to point out that the prior art the Defendants have raised in front of you to establish a substantial issue is art that was considered by the patent office. That does not end the inquiry. Looking at the case law, you still have to assess the arguments that they make.

But what the cases teach us, Your Honor -- and you can see it. I just put it here for your benefit where these things are cited from the patents. It makes it harder to meet that clear and convincing evidence, if you will, if you start -- the hurdle is here, and normally maybe you start here. You start lower, if you will, because the PTO has

already looked at this and has granted some deference; right? That's' why presumption exists. And if the arguments are essentially the same, the factfinder should be skeptical that the conclusion being offered is correct. It's not impossible, that's not what I'm saying, but skeptical. That the conclusion based on prior art record raising essentially the same arguments that were raised at the PTO, and that the PTO somehow just made a mistake. Different when you don't have the prior art in front of you.

So these cover essentially, as I've grouped them, methods for ruling out common benign alterations in the gene. And we talked -- I read the tutorial that talked about mutations, and then there's also polymorphisms, which are benign, things that don't cause any problems but nonetheless differencees in the sequence from the wild-type genes.

And what these claims do essentially, Your Honor, is assemble the most common sequences that are benign so that you can quickly rule out, as it were, oh, I've got a difference from the wild-type. Oh, thank goodness, it's one of the common benign polymorphisms so, therefore, I don't need to be worried about it. Essentially that's what the claims cover in different ways.

They talk about if you see something different from the benign polymorphisms, then you should be worried about that and investigate, as it were, whether or not that's a mutation

of concern. So it's a -- if you will, a quick and easy way of ruling out those changes in the sequence that aren't of concern. It's really just that simple.

And the reason they're not obvious under the prior art that's of record, and the reason examiners found the same, is the prior art did disclose a couple of these benign polymorphisms, but disclosed a bunch more than I recited, so it wasn't known which ones were the most common, but it also did not disclose others that are in the claims. So in essence what the invention is is a combination of the seven that lead to the quick, if you will, quick result that these things are not to be worried about.

Skilled artisans could not have reasonably expected that combination would define, if you will, as we put it, the benign signature of the claimed consensus sequence. That's what we were looking at, sort of the benign signature that's any one of these seven or any combination of them.

This is what the patent office said, Your Honor, in allowing the claims, essentially the same thing. The art did not suggest, and there's the same references again, that a consensus sequence limited to a specific set of seven neutral polymorphisms, and did not suggest excluding others, such as taught by Skolnick, to arrive at those selected from -- selected in the claim.

So in looking at this invention, what you're looking for

is it obvious to come up with the combination in the claim? Not is it obvious to try to test it for polymorphisms? I think that's the argument. The question is is it obvious to come up with these seven as the benign signature? And I don't think they've come close to showing with prior art of record that that is the case.

That's it, Your Honor, on obviousness. Two minutes on written description, the other argument raised. It's very lightly touched on, but it's in their brief, and I said I would try to touch on the things that are in their brief.

Written description most typically, Your Honor, is a defense of you saw what I was doing in the marketplace. You changed your patent to try to cover me, and so therefore what you now are claiming it's not there in your patent. Usually that's sort of the standard -- I was trying to figure out a way to describe it. Sort of you've got -- patents are property. And I like to look at regular property. It's easier to understand. And, you know, if you will, you've moved the boundary of your deed, and it's different than the description of the deed. You're saying this is my property, but your deed describes it within these metes and bounds, so you can't do that.

And the deed in this case, description of the metes and bounds, is the patent specification, and we look at it. But we don't have to get down in the weeds or into that -- those

trees because the Defendants are relying essentially on an erroneous claim construction. They're reading out the word potential. Do you see there, Your Honor, we underline it at the end? What they say is, well, the patent doesn't disclose the mutations that do correlate with increased susceptibility. And, you know, there's some disclosure in the patent and we could argue about that, but that -- for purposes of this proceeding, that's just the wrong way of looking at the claim.

The claim talks about that you're trying to avoid these benign -- excuse me -- understand the benign signature, so if the mutation is different, or the difference in sequence is different than the benign signature, then you might have a potential problem and you need to go investigate. Essentially, like I said, a quick way to let those in the field determine that an alteration might be a problem. They have to go then figure out whether it is a problem. But a quick way to determine whether something might be a problem or whether most commonly it's not a problem.

And, again, that's exactly the reading of the claims that the examiner put, wherein the presence of the mutation, other than the polymorphisms recited in the claim, is neutral is correlated with the potential of increased genetic susceptibility to breast or ovarian cancer. And then in parens the examiner says mutations identified will still have to be tested to determine whether they are themselves neutral

or causative.

So there's no requirement that the patent actually disclose the mutations. The whole idea is to identify those that might be problematic. The written description defense of Defendants rests on erroneous claim construction, right where we started on the anticipation defense earlier.

Your Honor, that's all I have. I'm happy to answer any questions, but if not, I'm sure Mr. Swedlund would love to come testify for you.

THE COURT: Why don't we hear from him.

MR. SINGER: Okay. Let's get him. And, Your Honor, my examination will be on the order of three or four minutes I think.

The Court: Take your time. We're here to hear what the parties have to share with us.

MR. SINGER: And, Your Honor, Just one note for the record as we wait for Mr. Swedlund. We realized last night as we were getting ready that there was actually -- says -- my note here says chicken scratch. There was a little writing on the back of one of the pages of the attachment to Mr. Swedlund's declaration that we did not file, and we did not notice it until last night. We provided it to opposing counsel. We can file it if the Court wants or we can just go with what he has without it. It's up to the Court.

THE COURT: I don't need to see it unless Mr. Gaede

thinks there's something of significance in it.

MR. GAEDE: If they think there is.

Mr. Singer: I don't.

MR. GAEDE: I didn't see it last night.

MR. SINGER: Chicken scratch is really good.

THE COURT: We'll leave the record as it is then. Why don't you come forward, sir. We'll have you sworn.

The CLERK: Please raise your right hand.

(BRAD SWEDLUND, PLAINTIFFS' WITNESS, SWORN)

Thank you. Please be seated. Please state and spell your name for the record.

THE WITNESS: My name is Brad Swedlund, S-W-E-D-L-U-N-D.

DIRECT EXAMINATION

BY MR. SINGER:

Q Good afternoon, Mr. Swedlund. If you could just introduce yourself to the Court we'd all appreciate it.

A As I said, I'm Brad Swedlund. I work for Myriad Genetics as a scientist.

Q And how long have you worked at Myriad?

A For just about 18 years now.

Q Okay. And are you the same Brad Swedlund that swore out a declaration in this matter?

A That's correct.

Mr. Singer: Okay. Permission to approach, Your

Honor?

THE COURT: Please.

Q (BY MR. SINGER) Mr. Swedlund, you have -- or Swedlund, get that right, you have a document in front of you captioned Declaration of Brad Swedlund. Is this the declaration you swore out in this case?

A Yes, it is.

Q And is that your signature at page three of the declaration?

A Yes, it is.

Q Okay. Does this declaration accurately reflect the testimony you've already given in this proceeding?

A Yes.

Q And do you understand it to be as if you had just testified to the matters contained therein?

A Okay, thank you, yes.

Q Okay, thank you. When we did your declaration we neglected to tell the Court about your educational background. Maybe you could do that, sir.

A I have Bachelor of Science degrees in biology and botany from South Dakota State University, and a Master's Degree in botany from the University of Florida.

Q And before coming to Myriad in 1995, were you employed, sir?

A Yes, at Agridyne Technologies here in Salt Lake City.

Q And what did you do there at Agridyne?
A I worked on molecular genetics, transformation of plants mostly.
Q At Agridyne did you learn techniques of molecular biology?
A Yes, that and in college also.
Q Okay. In your declaration you say that when you came to Myriad you began working with a team of scientists whose goal was to identify the BRCA2 gene, and that's in paragraph two of your declaration if you need to refer to it. Just tell the Court if you could what generally you did on the BRCA2 discovery team.
A When I first came to Myriad I worked on what we call genomic walks where we would try to connect jumps of genomic sequence that we had found by using -- developing primers and then doing PCR and sequencing to see if we could connect the pieces.
Q As part of that project did you and the team regularly generate records as part of your work?
A Yes, we did.
Q Were the records electronic or paper or both?
A Both.
Q Were those records to your knowledge kept at Myriad as part of Myriad's business?
A Yes, they were.

Q The Exhibit-A attached to your declaration, just so it's clear, what type of document is that? What are we looking at there?
A It's the output from a computer program that we used at Myriad.
Q And what's the name of that program?
A It's called Sequencher. That's with a C-H-E-R.
Q Is that a program that you worked with at Myriad in 1995?
A Yes, I did regularly.
Q Was it used by the BRCA2 team to your knowledge?
A Yes.
Q Okay. Did you ever print out documents from Sequencher?
A Oh, yeah, yes.
Q Do they look like Exhibit-A when you print them out?
A Very similar, yes. Different sequences of course, but, yeah.
Q We showed the Court the date stamp. Do the documents you printed out normally have a date stamp?
A Yes.
Q And is that the date printed or the date that whatever is being reflected in the document was undertaken?
A It would have been the date the document was saved, and then the date -- doesn't reflect the date it was printed,

no.
Q All right. Where did you locate Exhibit-A?
A In some archive files that belong to a previous employee of Myriad, Dr. Sean Tavtigian.
Q And how are those archive files stored?
A They're stored in a storage room at Myriad Genetics.
Q And what is kept in those archives in your experience?
A Lots of materials related to past projects, papers, things like that.
Q Have you gone into that archive to find documents prior to this case?
A Yes I have.
Q Are these -- do you rely on those documents in your work at Myriad when you need them?
A Yes, when I need them.
Q Are those documents stored, or used by Myriad, excuse me, in its daily business to your understanding?
A Yes, as I understand, yes.
MR. SINGER: Pass the witness, Your Honor.
THE COURT: All right, thank you.
Mr. Gaede.

CROSS-EXAMINATION

BY MR. GAEDE:
Q Mr. Swedlund, a couple of questions for you. The document that you identified, you were not there at Myriad at

the time it was generated to the best of your knowledge; correct?

A That's correct. I started in September of that same year.

Q Okay. And it's true that when you started in September, Myriad did not know the sequence of the BRCA2 gene; correct?

A That's correct. We didn't know that it was -- any specific gene was BRCA2.

Q Right. You knew it was in the 1.5 -- approximately 1.5 centiMorgan range; correct?

A You're testing my memory on the actual size, but that's -- that sounds about right, yes.

Q Okay. And then from that you were using approaches that had been used in locating the precise location of the BRCA1 gene; correct?

A Yes.

Q And you were using positional cloning techniques that had been used for BRCA1 that were being used for BRCA2; correct?

A Yes. They were common to all positional cloning projects I believe.

Q Okay. And the two primers that are shown in the exhibit that you have attached, to the best of your knowledge, at the time when you joined Myriad in September of 1995, myriad did not know that they were priming a sequence of the BRCA2 gene; correct?

A If I may correct part of that.
Q Sure.
A So there's actually four primers listed on -- in document Exhibit A, is it? The sequential file, and then there's two primers there listed in the following exhibit. And so I think -- could you repeat your question, I'm sorry.
Q Sure. So there was four primers in the first exhibit?
A Yes.
Q Okay. And are they separate primers in the second exhibit, different set of primers?
A In the second exhibit it was just a demonstration of how those primers would align, so that was my own alignment --
Q Right. It's one of the set in the first --
A Yes, they were part of the first set.
Q All right. Got it. So let's take the set that you used in your Exhibit B.
A Okay.
Q At the time when you joined Myriad in 1995, September 1995, Myriad did not know that those primers would prime a PCR reaction to amplify a portion of the naturally occurring BRCA2 sequence; correct?
A We knew that it primed a gene within the BRCA2 region. We didn't know necessarily that it was specifically a BRCA2.
Q Okay. So you knew it primed a gene in the region, you just know specifically that it wasn't the BRCA2 gene section

that was being primed and amplified; correct?
A That would be correct.
Q I'm sorry?
A That would be correct, sorry.
Q Thank you. And the same is true for the other set of primers in your Exhibit A?
A Yes.
MR. GAEDE: If I may, Your Honor, just one question for my colleague and then --
(Brief Pause)
Thank you so much, sir.
THE WITNESS: Thank you.
MR. SINGER: No redirect, Your Honor.
THE COURT: Thank you, Dr. Swedlund. You're welcome to step down if you'd like.
Mr. Singer, anything more from you?
MR. SINGER: Nothing from me, Your Honor. Our next module, if you will, is Dr. Kay, if the court would like to hear from Dr. Kay. I don't know that they can finish their direct, maybe they can, today. It's unclear.
THE COURT: Well, I think -- I think we need to afford the Defendants an opportunity to respond to the Plaintiffs' presentation in this module before we move on to the next one.
MR. SINGER: Okay. This is part of the module, so I

think this is --

MR. GAEDE: This is the time to call him and, you know, we'll stipulate to he's an -- stipulate to his qualifications and his declaration is true and correct testimony in the best of his ability so I can start crossing. We'll be done by 5:00 o'clock.

THE COURT: All right.

MR. GAEDE: And then we can go into our presentation tomorrow morning.

THE COURT: That's fine with me. And, Mr. Singer, does that present an issue for you?

MR. SINGER: No, it certainly doesn't, Your Honor.

THE COURT: I'm sure Dr. Kay would like to get finished with this today. Why don't we call him.

MR. SINGER: And, Your Honor, my colleague, Geoff Biegler, is going to be presenting Dr. Kay.

The COURT: The name one more time.

MR. SINGER: Geoff Biegler, B-I-E-G-L-E-R. He's appeared and should be noted in the record.

THE COURT: Thank you.

The CLERK: Please raise your right hand.

(MARK ALLAN KAY, PLAINTIFFS' WITNESS, SWORN)

Thank you. Please be seated. Please state and spell your name for the record.

THE WITNESS: Mark Allan Kay, Mark, M-A-R-K, Allan,

A-L-L-A-N, Kay, K-A-Y.

MR. BIEGLER: Your Honor, we have binders with a few exhibits in them, if I may approach?

THE COURT: I would be disappointed if you didn't.

MR. BIEGLER: May I proceed, Your Honor?

The COURT: Please do.

MR. BIEGLER: I'll try to -- I understand defense has stipulated to Dr. Kay's credentials so we'll try to make this fast, but we'll try to introduce him at least --

MR. GAEDE: Your Honor, seriously, if we're stipulating, I don't see the need to spend time here on this.

MR. BIEGLER: Your Honor, I think Dr. Kay does have some new comments in light of the declarations that were submitted last Friday by Dr. Bowcock and Dr. Gregory, so we were planning on providing some testimony in response to that.

THE COURT: Well, it's --

MR. BIEGLER: And we notified Defendants' counsel of that I think yesterday, so they were aware of this.

MR. GAEDE: Your Honor, this is the first I've heard of it, and admittedly yesterday was a little bit of a blur. It's the first I've heard of it. This clearly contravenes the Court's order in terms of the testimony is through the declarations and then cross-examination.

MR. BIEGLER: Our position, Your Honor, is that the

Court didn't anticipate getting brand new fact expert declarations on Friday night which were close to 100 pages for the ones relevant to Dr. Kay, and he has not had a chance to respond to those new opinions from Defendants' experts. We'll be planning to present today's brief that's only about 20 minutes or so.

MR. GAEDE: Object, Your Honor.

MR. MANGUM: Well, I would indicate for the records, David Mangum, that we did in fact communicate to them, as we were discussing which witnesses would be called, that we intended to have Dr. Kay address and respond to the supplemental declarations and any additional information that came from those, and Mr. Gaede at the time said he would reserve his objection about that.

THE COURT: The subject matter, Mr. Biegler, briefly?

MR. BIEGLER: There's a large amount of subject matter in Dr. Bowcock's and Dr. Gregory's declaration, but I think Dr. Kay wants to respond to the comments on linear PCR with respect to the deposit markers and some of Dr. Bowcock's comments about the predictability of gene discovery and some of the techniques that were used by the inventors and others in the field.

THE COURT: Mr. Gaede, I'm going to hear this evidence. We have the witness here. I understand that you

haven't had an opportunity to receive it and review it. We have by necessity, because of the pace at which we've all been moving, been dealing with I think a fluid situation. This is unlike most of our instances where the record's clearly defined well in advance of a hearing. That's just a necessity borne out of the urgency of this issue.

I think -- I think we'll allow the Plaintiffs an opportunity to respond to those declarations that were received late last week. You'll have a chance to consult with your colleagues overnight because we'll break after we hear this direct testimony. Your objection is noted.

MR. GAEDE: Thank you, Your Honor.

THE COURT: Thank you. And I don't think it will be necessary, but if it is, if you think that there's something further to address by way of testimony from one of your experts and he's -- he or she is here tomorrow and you want to put them on the stand, let's have it out. That's what we're here to do is to hear from the witnesses.

So, Mr. Biegler, go ahead.

MR. BIEGLER: Thank you, Your Honor.

DIRECT EXAMINATION

BY MR. BIEGLER:

Q Dr. Kay, what do you do for a living?

A I'm a professor of pediatrics and genetics at Stanford University.

Q And how long have you been a genetics professor at Stanford?
A Since 1998.
Q So approximately 15 years?
A That's correct.
Q Have you been asked to provide opinions about the validity of the patents asserted in this case?
A Yes.
Q And have you also been asked to respond to the declarations of Doctors Bowcock and Gregory submitted on behalf of the defendants?
A Yes.
Q Have you in fact formed opinions if the patents asserted are valid?
A Yes.
Q And you submitted a declaration that contained those opinions?
A Yes, I did.
Q Okay. If you could turn to tab one in your binder.
A Uh-huh.
Q Is that the declaration that you submitted in this case?
A Yes, it is.
Q Does it accurately reflect all the opinions you have to date in this matter?

A It reflected my opinions as of August 30th on prior to receiving additional declarations after last Friday.
Q And you just heard between the attorneys and the Court you have new opinions or at least responses to some of what was said in the new declarations?
A Yes, that's correct.
Q Okay. Just briefly before we get into that, I'd like to just go over your credentials at a very high level. I've been calling you doctor. Are you an M.D. or a Ph.D.?
A I'm an M.D. and a Ph.D.
Q You hold both degrees?
A Yes, I have both.
Q And where did you get those degrees from?
A Case Western Reserve University.
Q How did you manage to get both a Ph.D. and an M.D. from Case Western?
A I was enrolled in the Medical Scientist Training Program, which is a duel degree program to train physician scientists.
Q And how many years have you conducted research and been teaching in the field of genetics?
A Since the early 1980s.
Q So 30 years?
A Yes.
Q Before Stanford where did you teach?

A I was at the University of Washington in Seattle.
Q Okay. And how many peer reviewed articles have you published in the field of genetics?
A Over 200.
Q And how many journals in the field of genetics are you affiliated with?
MR. GAEDE: Your Honor, object. We stipulated and, you know, our time is limited.
MR. BIEGLER: We're almost finished, Your Honor, if you'd just indulge for another question or two.
THE COURT: All right. Go ahead and wrap it up. This is information that's contained in his reports already.
THE WITNESS: I'm the associate editor of one journal and on the editorial board of several others, and do peer review for a number of journals.
THE COURT: I don't believe anyone is taking issue with Dr. Kay's credentials.
Q (BY MR. BIEGLER) Your current C.V. is attached to the declaration; correct?
A Yes, correct.
Q Thank you. We're going to go through a summary of your opinions in the declaration, but if we can fast forward past that for a second time. Have you formed new opinions since receiving the declarations of Dr. Bowcock and Gregory?
A Yes.

Q Have you reviewed those declarations?
A Yes.
Q Okay. Let's talk first about Dr. Gregory's opinions -- sorry, I'm going to skip forward a little bit here. Did you review Dr. Gregory's comments on linear PCR?
A Yes, I did.
Q Okay. And do you agree with Dr. Gregory that the claims at issue, the primer pair claims, cover lineal PCR?
A No, I do not agree with Dr. Gregory's opinion.
Q And just looking at the language of the claims that we put up here on the slide, what's the first reason that you think the claims do not cover linear PCR?
A Well, linear PCR involves the use of a single-stranded DNA primer for determination of a nucleotide sequence, and PCR involves the use of a primer pair for amplification.
Q Does the language PCR standing alone have any connotation to you?
A PCR standing alone, especially in the years -- in the mid 1990s and even now generally refers to routine or regular PCR.
Q So without any modifier, you understand it to refer to regular PCR?
A That's correct.
Q Okay. And the additional language in the claim that refers to a single-stranded pair of DNA primers, that also

supports your conclusion?
A Yes, it does.
Q And why is that?
A Well, because a pair of single-stranded DNA primers in a single reaction is really what the definition of general or regular PCR would be called.
Q So you wouldn't use double-stranded DNA in a linear PCR reaction?
A That's correct.
Q Did you have a chance to review the references that Dr. Gregory cited on linear PCR?
A I did have a chance to review those.
Q Did those change your opinion in any way?
A No, they did not.
Q Okay. Let's first talk about the Rosenthal article that was cited. And if you'll turn to -- it's tab 6 in your binder -- I'm sorry, two.
A Yes.
Q Is that the Rosenthal paper that Dr. Gregory relied on?
A Yes.
Q What does the Rosenthal paper disclose at a high level?
A The Rosenthal paper describes a process of genomic walking and sequencing using a process of linear PCR.
Q Does Rosenthal disclose the use of a double-stranded DNA fragment in a PCR reaction?

A No.
Q What does it disclose?
A It discloses the use of a single-stranded primer for DNA amplification.
Q And here you've put in your slides a blowout of a figure from the Rosenthal paper. Can you explain what that shows, and especially the highlighted portion.
A Right. So the process here is a way to identify DNA sequences, and in this process genomic DNA is cleaved and a single-stranded primer is then used in a region where one knows of the sequence and then does an amplification step to actually elongate past the known sequence into unknown sequences.
Q And so the language you're looking at there is where it says a linear PCR with only one biotin-labeled specific primer --
A That's correct. So in this case you are not using a pair of primers, you're using a single strand of DNA.
Q Okay. Let's turn next to the Murray paper that Dr. Gregory cited. And if you turn to tab three in your binder, what's tab three? Is that the Murray paper?
A Yes.
Q What does the Murray paper disclose at a high level?
A Yeah. So the Murray paper describes again another use or modification of linear PCR where you're using one

oligonucleotide as a primer to identify a sequence of a region of DNA.

Q So, again, the Murray paper does not show the use of a double-stranded DNA fragment in a linear PCR?

A That's correct.

Q Let's move on. Now, did you review Dr. Bowcock's discussion of the literature about the possible regions where the BRCA1 gene might be located?

A Yes, I did.

Q Okay. Did Dr. Bowcock's comments change your opinion on obviousness at all?

A No, they did not.

Q Can you tell the court why not, please.

A Well, I mean there's a lot of points at issue here, but the fact is that at the time of the discovery of the BRCA1 gene, there was still some debate in the -- in the literature about the region that actually the gene actually fell into, and even if one debates about which range is correct or not correct, even the smallest range still was quite large and there was still no obvious way to go about it to identify that sequence.

Q Do you recall how big the range was for the -- the smallest range identified by Dr. Bowcock?

A I believe it was in the range of six centiMorgans.

Q Approximately how many base pairs?

A That would be 6,000,000 base pairs.
Q So why would it not be obvious to locate the BRCA1 gene even starting from a region of five or six centiMorgans?
A Well, the point is that even within a six centiMorgan region there were clearly hundreds of genes that were in that region. So then the question is how do you identify a gene for which you have no known information about the protein or where and how it's expressed.
Q Was the route from that region predictable or unpredictable?
A Oh, it's absolutely unpredictable because how would one know which gene it was in that group?
Q So let's talk a little more briefly about the predictability of gene discovery in this time frame. Did you also read Dr. Bowcock's assertion that the techniques and the methods of gene discovery were routine and predictable?
A Yes, I did.
Q I take it you don't agree with it?
A I disagree with that.
Q Okay. Do you have examples that show how unpredictable gene discovery can be?
A Well, one of the examples listed in Dr. Bowcock's declaration is the use of positional cloning to identify the cystic fibrosis gene, and in fact positional cloning technologies and techniques were used to identify the gene,

but the first identification of the gene that was published in Nature, a very high profile journal, turned out to be incorrect.

Q And if you could turn to tab four of your binder, please. Can you tell me what -- what's in tab four.

A Right. So in tab four was a publication in April of 1987 in Nature in which a candidate gene for C.F. was identified based again on a number of different positional cloning technologies, and it turned out that this was -- turned out to be not the correct gene.

Q And does the C.F. example, does that -- what does that tell you about the predictability of gene discovery?

A I mean that makes it clear that it's not predictable because even when you have a range whittled down, it's still hundreds and -- depends on the range, could be hundreds, thousands of genes in that region, and still the way to go about identifying it isn't so -- isn't predictable or clear-cut.

Q Do you recall how much time passed before they realized that it was the wrong gene?

A Yeah, I believe it was five or six years.

Q Now, do you recall that Dr. Bowcock also mentioned --

MR. GAEDE: Your Honor, I object again to this whole line of inquiry. This was addressed in his reply declaration, and this subject matter he's now testifying here in court has

already been dealt with by him in his reply.

THE COURT: It's overruled. We're going to take a short amount of testimony on this point. You'll have a chance to address it with Dr. Kay in the morning.

MR. BIEGLER: Thank you, Your Honor.

Q (BY MR. BIEGLER) Dr. Kay, do you also recall Dr. Bowcock in her supplemental declaration talk about the search for Huntington's disease and the example that provided with respect to the search for BRCA1?

A Yes, I do.

Q If you could turn to tab five in your binder, please. And what's tab five?

A Tab five is a paper describing a novel gene that was identified in the Huntington -- for Huntington's disease.

Q Why do you think the Huntington's example is relevant here?

A Well, the Huntington's disease gene was a gene for which people had localized to a specific region on chromosome 4q, but it still took 10 years to actually identify the gene itself.

Q So we put a little blowout on the slide here that shows -- can you explain what the first clause that we have there shows?

A The -- well, first of all, that the gene is identified on Huntington's disease chromosome, but the genetic disease

causing Huntington's disease was assigned to this chromosome 4 back in 1983 but it wasn't until 1993 I believe that it was actually identified, so a 10 year period.

Q And what does that tell you about the predictability or unpredictability of gene discovery?

A Again, that makes it unpredictable.

Q Did the search for Angelman syndrome influence your opinion at all?

A Yes. And that's another interesting disease where people had it narrowed down to a very specific region, and in fact there were a lot of known genes that had already been identified in that region. And in fact when people found that region, they looked at a couple genes that they thought would be prime candidate genes, but based on the way those genes were being expressed, they actually ruled it out as the candidate gene because it wasn't expressed in the way one might have predicted based on the phenotype of that particular disease.

But it turns out four years later the gene -- one of the genes they actually dismissed turned out to actually be the gene because they didn't really understand the expression patterns as well and, you know, in hindsight it makes a lot of sense now.

Q If you can look at tab six and seven of your binder. I think those were the papers you wanted to show with respect to

Angelman syndrome; is that correct?

A That's correct.

Q Okay. And if we look at the slide, you've blown out some portions of each paper, and can you just explain what this shows to the court.

A Right. So in the first paper that was published in Human Molecular Genetics in 1994, it basically says based on the biological information for the gene called E6-AP, and on the imprinting analysis of this gene and then another gene, which were thought to be strong candidates for causing Angelman syndrome, but it turned out neither -- neither -- that in the end it -- this particular -- these particular genes were thought not to be involved in this disorder because of the expression pattern.

Q So first they thought this E6-AP gene was not the right one, and three years later they realized it was the correct one?

A That's correct.

Q How does Dr. Bowcock's -- Dr. Bowcock and chromosome 13 play into your analysis?

A Well, Dr. Bowcock in 1990 published a manuscript that actually suggested that chromosome 13q was an unlikely candidate region for a BRCA gene locus.

Q If you could turn to the next tab of your binder, please. It's tab eight. Is that the tab that you were -- that you

were referring to?
A Yes, it is.
Q We've blown out part of that paper. Can you just explain to the Court what the blowouts are showing.
A So there was some thought at the time again that 13q may encode a locus for a human breast cancer gene locus. But based on the studies that they did, they looked at some expression profiles on cells from patients and from human breast cancer tissues, and based on that analysis they were looking at a particular cancer causing gene that was in that region, and then what they concluded in the end when they were able to determine that that wasn't the actual gene causing locus, that then they concluded that chromosome 13q is unlikely to be the site for the primary breast cancer gene.
Q And eventually the BRCA2 gene was identified in chromosome 13q; correct?
A That's correct.
Q And does that indicate to you that the art of gene discovery for the relevant time was predictable or unpredictable?
A Oh, that's again unpredictable.
MR. BIEGLER: Thank you. That's all I have.
The Court: All right. We've had a -- we've had a good, full day today. We have more to cover tomorrow. What do we have to cover tomorrow?

Dr. Gaede -- I keep trying to do that.

MR. GAEDE: Just an English major, Your Honor.

THE COURT: Mr. Gaede, you'll have a chance, of course, to conduct some cross-examination of Dr. Kay, and then I gather you have a response to obviousness and anticipation and the like, and then where are we after that?

MR. GAEDE: And we'll move right -- we'll move quickly through that, and then we're into the three, what I'll call, equitable factors with the presentation by both sides plus Mr. Ford's testimony. I would ask Your Honor, since the witness is currently under oath, that it would be improper for him to discuss his testimony in any way even with attorneys and he should be so instructed.

THE COURT: Well, what would be the basis for an instruction to this witness as an expert that he not communicate with his lawyers or with --

MR. GAEDE: Well, right now he's under oath and he's testifying in this court.

THE COURT: Well, he'll be under oath tomorrow and he'll offer honest answers to your questions. I'm confident of that. I am going to instruct you, Dr. Kay, not to discuss your testimony with anyone except counsel for the Plaintiffs until after we conclude sometime tomorrow.

THE WITNESS: Okay, thank you.

The Court: All right. Your estimate, counsel,

about how much time we need tomorrow?

MR. MANGUM: Your Honor, I think that probably -- and I don't know how long their presentation with regard to validity issues would be, but I would think that the equitable factors we could do quite quickly, that our presentation would probably be on the order of a half-an-hour. Then Mr. Ford will be put on the stand very briefly by us just to lay the foundation for his declaration, and then turn it over for cross-examination.

MR. GAEDE: And I don't anticipate a long cross-examination of Mr. Ford in the subsequent presentation. Perhaps if we could -- is there a time that the court would be finished if we could perhaps start a half hour earlier at 9:00? I'm sure we'll be done by noon.

The Court: Well, I thought we could, and then we ended up with a matter, a criminal matter, that could only be set tomorrow morning at 10:00 o'clock, and so we'll be proceeding with that. It's a sentencing that involves four related cases in four different states and it just had to be done tomorrow. We'll be done before 11:00, and we'll have that completed and we'll clear the courtroom so we can start promptly at 11:00 here. And then I'm free until another sentencing at 2:30. And then the afternoon is booked. So I have between 11:00 and about 2:30. And if we need to go over to a third day, then we'll do that. But can we conclude in

three-and-a-half hours tomorrow if we go through lunch?

MR. MANGUM: I believe that we can.

MR. GAEDE: Yeah, if we work right through lunch, I don't see why we can't.

THE COURT: So we'll be hungry and mean but we'll be done?

MR. MANGUM: That's the way we like it.

THE COURT: All right. I think that's what we'll do then. Is there anything else we should take up while we're all here today?

MR. MANGUM: Nothing that I'm aware of, Your Honor.

MR. GAEDE: No, nothing, Your Honor.

The Court: I appreciate your hard work today and your organization, counsel. We'll be in recess.

(Adjourned at 5:00 pm)

* * *

Certificate of Reporter

I, Raymond P. Fenlon, Official Court Reporter for the United States District Court, District of Utah, do hereby certify that I reported in my official capacity, the proceedings had upon the hearing in the case of University of Utah Research Foundation, et al. Vs. Ambry Genetics Corporation and Gene By Gene, case No. 2:13-CV-640RJS, 2:13-CV-643, in said court, on the 11th day of September, 2013.

I further certify that the foregoing pages constitute the official transcript of said proceedings as taken from my machine shorthand notes.

In witness whereof, I have hereto subscribed my name this 19th day of September, 2013.

/s/ Raymond P. Fenlon